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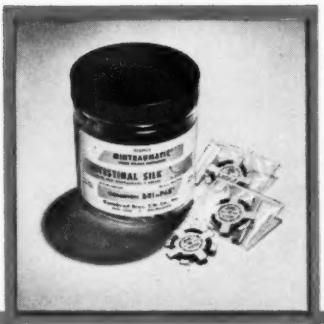

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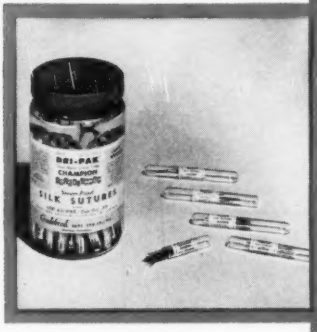

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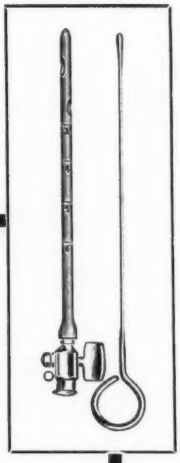

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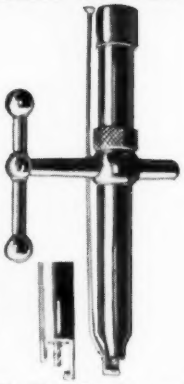

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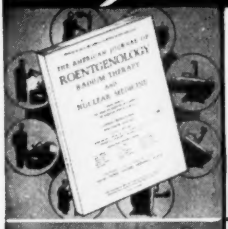

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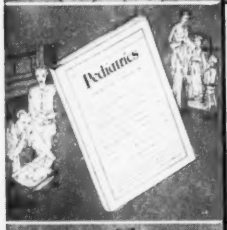

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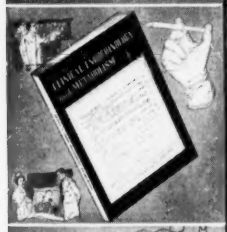

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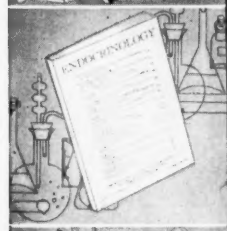

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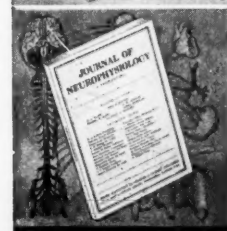

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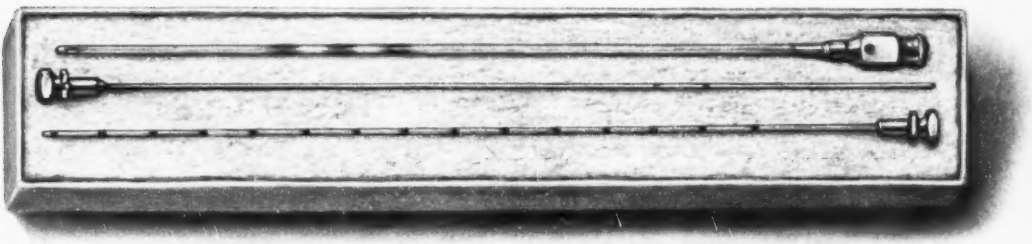

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*Cooper, I. S.: Chemopallidectomy: An Investigation Technique in Geriatric Parkinsonians, Science 121: 217-218 Feb. 1955.

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Neurosurgical Centre, Brook Hospital, Woolwich, and Department of Applied Physiology, Royal College of Surgeons of England, London, England

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UNTIL recent years the attention of those concerned with the management of intracranial abscesses has been largely directed to a study of the findings in mortal cases.[1,2,5,8,9,12,15,17,18,20,24,26,27,30,32,33,41,51,53,54,60] But now that antibiotic therapy and improved surgical techniques can reduce the risk of death from this dread disease from over 70 per cent to about 25 per cent[1,4,6,7,17–19,24,27,28,31–33,41,42,49,52,54,57,60,66] the morbid—rather than the mortal—consequences of cerebral abscess formation assume increasing importance.

Among these consequences, the three principal disorders that may mar the life of a patient surviving after treatment of a cerebral abscess[8,18,60] are pareses, mental disorders and seizures† (Table 1). These disorders, in the series of cases reported in this communication, occur respectively in 25 per cent, 25 per cent and 47 per cent of the cases of successfully treated brain abscesses. Of all the complications of survival, seizures are therefore the more common, occurring sooner or later in almost half of the patients surviving after treatment of an intracerebral abscess.

Our object, then, in this communication is to arouse interest in the clinical and pathological problems of post-abscess seizures, which form the most important complication of what otherwise may be satisfactory recovery from the disease. For it seems to us that if the principal provocative factors in this connection can be identified, an attempt might be made to eradicate or alleviate them in the course of surgical treatment.

CLINICAL MATERIAL

The clinical material forming the basis of this study is drawn from a series of 100 consecutive cases of intracranial abscess treated, during the past 8 years, in the Neurosurgical Centre of the South-East Metropolitan Region. Twenty-three of these patients had abscesses confined to the cerebellum, and are not considered further here, as none of the survivors had

* A preliminary report of these findings was presented at the Second International Congress of Neuropathology, London, September 1955.

† In this communication the term *seizure* embraces not only muscular convulsions (whether focal or generalised) but also all paroxysmal disorders of sensory and psychical function constituting "sensory seizures" and "psychical seizures."

postoperative seizures. Of the remaining 77 patients with supratentorial abscess, 12 had subdural abscesses alone, while 65 had one or more intracerebral abscesses—and it is to this latter group that attention is principally directed. It should perhaps be added that 8 of the 65 patients with intracerebral abscess had multiple lesions, while 5 had a subdural as well as an intracerebral abscess.

The regional distribution of the intracerebral abscesses in the brain is indicated in Table 2. The multiple abscesses involved these same regions of the brain, with additional abscesses in structures of the brain stem in 1 case. In 22 per cent of the cases the abscesses were multilocular.[24]

Most of the intracerebral and subdural abscesses in this series were treated[6,17,19,24,27,32,33,52,55,57,60,66] by repeated puncture through burr-holes, with aspiration of their contents and instillation of the appropriate antibiotics together with radio-opaque material (either Thorotrast or Pyelosil). The choice of antibiotics was governed by estimation of the sensitivity of the organisms (in all cases except 5) to an array of antibiotics. Systemic therapy with antibiotics and/or sulphonamides was also provided, supplemented by intrathecal or intraventricular injections of antibiotic when necessary.[4,58,63] Anticonvulsant drugs were not given as a routine on discharge of the patient, being withheld until the development of seizure phenomena. Some of the subdural abscesses were drained through tubes inserted into multiple burr-holes, antibiotic solutions being instilled through these same tubes.[49] In a few of the earlier cases, an intracerebral abscess was also treated in this manner.[17] Excision of the abscess was performed in 3 cases only,[7,11,28] and in 1 case a frontal lobectomy (to include the abscess) was carried out.

Thirty-six of the patients with intracerebral abscess are still alive and available for study (a crude survival rate of 55 per cent[24,60]), as are 9 of the 12 with pure subdural abscess (crude survival rate 75 per cent).* Twenty-eight of the former group, and 6 of the latter group have outlived their illness by a year or more, 19 of those with intracerebral abscess having survived for periods in excess of 3 years. Ten of the surviving patients in the intracerebral group (28 per cent) now show no morbid sequelae of their illness whatsoever, although 4 of them did so temporarily. Five of the surviving patients in the subdural group (56 per cent) likewise are entirely normal, 3 of them having been so since completion of their treatment.

ANALYSIS OF MATERIAL

1. *General Incidence of Seizures.* The general incidence of seizures of all types after treatment of intracerebral abscess is 47 per cent (Table 1). The comparable incidence of seizures in cases of pure subdural abscess is 22 per cent. It is therefore apparent that the risk of the development of seizures following treatment of an intracerebral abscess is more than twice as great

* In a further 2 of the intracerebral cases the abscess recurred in its original site, after apparently successful treatment—an incidence of recurrence in the survivors[24] of 5 per cent. Both patients died, in spite of treatment.

as it is after treatment of a pure subdural abscess. Of the 5 patients with the combination of a subdural and an intracerebral abscess, only 2 have survived for a period of more than 6 months—but both of these have had seizures.

These findings indicate, then, that in almost half of all cases of intracerebral abscess seizures develop[8,18,22,24,29,32,39,61] at some period or another after successful surgical treatment. This incidence of seizures is of the same order as that obtaining with brain scars following penetrating injury of the head,[21,22,39,46–48,61,65] and with neoplasms in the brain.[21,22,35,39,64,65] The significance of the difference in the incidence of seizures after recovery from a subdural abscess and after recovery from an intracerebral abscess will be commented on later.

TABLE 1

Incidence of morbid sequelae in patients surviving after treatment of subdural and intracerebral abscess

Morbid Sequelae	Subdural Abscess Only	Intracerebral Abscess				All Intra-Cerebral
		Frontal	Parietal	Temporal	Occipital	
None (at any time)	56%	21%	0	31%	0	22%
Mental disorders	0	21%	50%	19%	0	25%
Muscular pareses	22%	14%	83%	13%	0	25%
Speech disorders	11%	7%	0	6%	0	6%
Visual disorders (including field defects)	0	14%	17%	13%	0	14%
Seizure phenomena	22%	57%	50%	38%	0	47%

2. *Regional Incidence of Seizures.* One of the factors that influences the development of seizures after recovery from an intracerebral abscess is the anatomical location within the brain of the original abscess[39,65] and of the scar that replaces it subsequently.

The correlation between the anatomical location of the abscesses in this series and the incidence of seizures of all types following recovery therefrom is indicated in Table 1. This reveals that 57 per cent of the patients with abscess in the frontal lobe eventually had seizures, as did 38 per cent of those with temporal lobe abscess and 50 per cent of those with parietal lobe abscess. No patient with an abscess of the occipital lobe in this series survived for a sufficient length of time for seizures to develop; although should such patients do so, seizures may occur in a small proportion of them, as is evidenced from series published elsewhere.[24,39,65] This correlation should be considered in the light of the regional distribution of the abscesses in the brain indicated in Table 2.

On the other hand, if attention be confined to those cases in which seizures developed after recovery it emerges that 53 per cent of the patients had had a frontal abscess, 35 per cent had had a temporal abscess, and 18

per cent had had a parietal abscess. As mentioned above, no patient with an occipital abscess survived to be included in the series of cases in which seizures developed.

These findings leave little doubt that with the methods of treatment described in this paper, the development of a frontal lobe abscess carries with it a considerable risk of seizures (3 chances in 5) when the patient recovers from his illness.[24, 65] The risk of seizures ensuing after recovery from a temporal lobe abscess is about two-thirds of that obtaining with frontal lobe abscesses; while the risk with a parietal lobe abscess is a little more than four-fifths of that with frontal lobe abscesses. The risk of development of seizures with abscesses confined to the occipital lobe is statistically negligible in comparison with the other sites, as is evidenced from figures from other sources.[24, 39, 65]

It is worth noting in passing that the incidence of seizures following

TABLE 2

Regional distribution of intracerebral abscesses

Location of Abscess	Proportion of Abscesses in Each Region
Frontal	31%
Parietal	21%
Temporal	40%
Occipital	7%
Multiple	11%

treatment of pure subdural abscesses (22 per cent) is only some two-fifths of that obtaining with frontal lobe abscesses, even though nearly all the subdural abscesses in this series lay in relation to some part of the frontal lobe—over its lateral, medial or orbital surfaces. In fact, of the 12 cases of pure subdural abscess there was only 1 in which the frontal lobe was not involved; this abscess lay beneath the temporal lobe in the middle cranial fossa.

These findings therefore leave no doubt that the risk of seizures developing after successful surgical treatment of an intracranial abscess is significantly influenced by the anatomical location of the brain scar that results from healing of the abscess. However, although there is a general impression,[24, 40, 62] arising largely from study of the effects of penetrating brain wounds, that scar formation in the frontal lobe carries with it a considerable risk of *status epilepticus* in addition to sporadic seizures, this correlation does not appear to obtain with brain scars following intracerebral abscesses. In the present series of cases, *status epilepticus* developed in only 2 patients following their recovery from an intracerebral abscess—and only 1 of these had had a frontal lobe abscess, the other having had an abscess in the temporal lobe. No patient with subdural abscess had *status epilepticus* as a late complication of recovery.

Nevertheless, the nature of the seizures that occur after treatment of an intracerebral abscess is influenced by the anatomical site of the brain scar that replaces the abscess. This applies, as with post-traumatic scars,[47,48,65] not only to the specific manifestations of the seizures but also to their general nature. For example, generalised seizures without focal manifestations are more common following treatment of frontal lobe abscesses, occurring in two-thirds of our patients with seizures. On the other hand, pure focal seizures are more common after operations for parietal lobe abscesses, although they also occur in half of those patients with temporal lobe abscess who had postoperative seizures. Focal phenomena as prodromata to generalised seizures occurred, in this series, only in the patients who survived after treatment of an abscess in the temporal lobe, being present in one-third of them.

Following recovery from a pure subdural abscess, none of our patients —as mentioned above—had *status epilepticus*. Instead, each of the patients with seizures displayed pure focal seizures only, with the exception of 2, who had rare generalised seizures as well. There were no cases of pure subdural abscess in which generalised seizures occurred with focal prodromata. This again provides an interesting contrast between the effects of an intracerebral frontal abscess and a subdural abscess over the frontal lobe, in that the usual seizure pattern following the former is generalised, without focal manifestations, whereas with the latter generalised seizures are rare, pure focal seizures being the usual pattern.

3. *Nature of the Infecting Organism.* Another factor that might influence the development of seizures subsequent to recovery from an intracerebral abscess is the nature of the infecting organism, and the method by which it has reached the brain. As a general rule[3,9,15,23,24,26,30,40,43,45,51,54,66] cerebral abscesses arise either by direct spread of infection from some part of the head into the cranial cavity, or by the passage of organisms from extracranial sources of infection into the brain by way of the cerebral circulation. Very occasionally (only twice in the present series of cases) an intracerebral abscess may result from a penetrating injury of the brain.

In the cases of the present series in which seizures developed after recovery, almost half of the abscesses were associated with middle ear infection, one-third were associated with sinusitis and one-fifth were associated with a pulmonary infection (usually bronchiectasis). In the remaining cases the abscesses were associated with blood-borne infections from a variety of other sites.

Organisms were cultured from the contents of the cerebral abscess in all cases except 5, in each of which the pus was sterile at the first and at all subsequent aspirations. Cultures were grown under both aerobic and anaerobic conditions.

In this series there is no statistically significant correlation between the frequency of occurrence of any one type of organism in the abscess and the subsequent development of seizures. In actual fact *Bacillus proteus*, *Strepto-*

coccus haemolyticus and non-haemolytic streptococci occurred with about equal frequencies in the cases in which fits developed. Likewise, there is no difference between the frequency of occurrence of any of these organisms in cases in which seizures developed after treatment, and those in which they did not. A variety of other organisms—including *Haemophilus influenzae, Bacterium coli*, various strains of *Staphylococcus aureus* and *Staphylococcus albus*, as well as *Nocardia*—were cultivated from abscesses in individual cases, in some of which seizures developed while in others they did not.

These findings indicate, then, that the bacteriology of cerebral abscesses is of little significance as an epileptogenic factor likely to influence the development of seizures after recovery from the abscess. And it may be relevant in this respect to note that, in cases of penetrating brain wounds, whether or not the wound becomes infected seems to have little influence on the risk of the development of post-traumatic seizures,[36] insofar as the proportion of infected wounds in patients with such seizures is very little different from that in cases in which they fail to develop.[46,47]

4. *Occurrence of Seizures Before and During Treatment.* In only 2 of the whole series of 100 cases in this series was there a history of seizure phenomena early in the life of the patient—that is, prior to the development of any intracranial infection. The occurrence of post-abscess seizures is not therefore dependent upon the fact that the patient has had seizures at some previous period in his life.

However, it might be that the possibility of the development of seizures following recovery from a cerebral abscess is related to their occurrence during the initial stages of the illness[62]—that is, during the period when the acute infection is establishing itself in the brain.

The influence of this factor is analysed in Table 3, in which the incidence of seizures of all types is considered in relation to the life cycle of abscesses in each of the major regions of the brain. It can be seen that about one-

TABLE 3

Occurrence of seizure phenomena in relation to life cycle of intracranial abscesses (excluding cerebellar abscesses)

Location of Abscess	Proportion of Cases with Seizures		
	Before Treatment*	During Treatment*	After Treatment*
Frontal	43%	30%	57%
Parietal	44%	19%	50%
Temporal	13%	17%	38%
Occipital	67%	0	0
All intracerebral	30%	20%	47%
Subdural only	67%	67%	22%

* "Treatment" refers to surgical treatment, which is taken to begin with the first aspiration of, or operation upon, the abscess, and to end with the patient's discharge from hospital. Some cases are represented under more than one heading.

third of the patients with intracerebral abscesses display seizures during the initial acute stage of formation of the abscess,[24] while one-fifth of them have seizures during the period when the abscess is establishing itself and the early reactions of the brain to its presence are developing. On the other hand, the incidence of seizures after recovery from the abscess is almost 50 per cent—that is, an incidence about twice that obtaining during the stages of abscess formation.

Further, these figures show that the incidence of seizures during development of a subdural abscess (67 per cent) is some three times as great as their incidence (22 per cent) after successful treatment of the lesion.

The reverse is the case with intracerebral abscesses; the incidence of seizures developing after recovery (47 per cent) is about one-half greater than their incidence during the stages of acute infection and two and a half times that during early development of the abscess.

These findings therefore suggest that the fibroglial reaction, which constitutes the essential part of the process by which a brain abscess heals,[10,36,39,51] contributes significantly to the occurrence of seizures after treatment by repeated aspiration. Relevant to this point is the fact that 77 per cent of the patients with intracerebral abscess who had seizures after treatment displayed their first ictal phenomena between 6 months and 1 year after completion of the aspirations.[24] This means that the reactions in the brain that are associated with the development of seizures require, in over three-quarters of the cases, at least 6 months to develop sufficiently. In contrast, the onset of seizures after treatment of subdural abscesses shows no such specific time relation, insofar as the date of the first seizure after completion of treatment is distributed quite at random.

Similar implications arise from repeated electroencephalographic studies of these cases (*q.v.*), in which the development of the brain scar and the emergence of local paroxysmal discharges can be followed.[34,39] With such methods we have found that there is steady progress in the fibroglial reaction around the initial site of the abscess for various periods of time during the first 6 months after treatment; but it is not until near the end of this period, in the majority of cases, that neurones in the vicinity of the primary cicatrix begin to display epileptogenic activity. These considerations obtain, irrespective of whether or not the patient has displayed seizure phenomena and paroxysmal disturbances in the electroencephalogram during the initial stages of development of the abscess.

5. *Influence of Methods of Initial Surgical Treatment.* In view of these findings, it would seem reasonable to suggest that if the development of the fibroglial reaction which inevitably occurs after successful treatment of a brain abscess by repeated aspiration could be minimised, the risk of later seizures might be diminished. From a surgical point of view, two aspects of treatment might contribute to this—one is aspiration of the abscess as early as possible after recognition of its presence in the brain; while the other is daily aspiration to produce rapid sterilisation and evacuation of the

abscess, so that its internal pressure remains low. This is apart from later excision of the healed cicatrix and its related glial extensions (*q.v.*).

(a) *Pre-operative interval.* The influence of the first of these factors may be examined by comparing the effect of varying intervals between the first signs of the presence of an abscess and the date of its first aspiration in cases in which seizures developed, and those in which they did not. Analysis of the dates of the initial aspiration in all the surviving patients shows that about one-quarter of them (26 per cent) were operated on during each of the first, second and third weeks after the first clinical evidence of the presence of an intracerebral abscess; while slightly less than one-quarter (22 per cent) were operated on for the first time after an interval of more than 3 weeks.

TABLE 4

Correlation between incidence of seizures and pre-operative interval*

Pre-operative Interval	Ratio $\frac{\text{Number of Patients with Seizures}}{\text{Number of Patients without Seizures}}$
1 week	1.0
2 weeks	1.7
3 weeks	1.2
More than 3 weeks	0.4

* The incidence of seizures in the group as a whole is almost 50 per cent.

$$\frac{\text{Number of patients with seizures}}{\text{Number of patients without seizures}} = 0.94$$

The ratio between the number of such survivors who had seizure phenomena and those who did not, for each of the above pre-operative intervals is given in Table 4.

These findings suggest that the interval elapsing between the onset of an intracerebral abscess and the time its surgical treatment is begun is related to the subsequent risk of seizures, insofar as a lapse of at least 3 weeks is associated with a seizure incidence after recovery that is about one-third (or less) of that resulting with earlier aspirations. Institution of surgical treatment during the second week in the life cycle of the abscess appears to carry the greatest risk of seizures when the patient recovers.

Although we have presented evidence (*vid. sup.*) indicating that the fibroglial reaction associated with the formation of the healing cicatrix might be an epileptogenic factor as far as late seizures are concerned, these figures suggest that it is not the reactions involved in primary encapsulation of the abscess that are responsible for the genesis of such seizures. For should the aspiration of the abscess contents and refilling with antibioties be delayed until encapsulation be established, then the seizure incidence is minimal on recovery.

In other words, it appears that it is the degree of extracapsular gliosis

and associated vascular disturbance that induces the abnormal activity in neurones in the vicinity of the abscesses that is eventually manifest as seizure phenomena.

This may perhaps explain why the incidence of seizures is about equal (*circ.* 50 per cent) with scars developing after abscess formation and after penetrating injuries of the brain,[39,46,65] but much less (4 to 10 per cent) with elective postoperative scars[13,14,39,50]—such as those produced by leucotomy procedures.* However, it is necessary to point out that whereas in about three-quarters of the cases of abscess with development of late seizures the onset of seizures occurs between 6 months and 1 year after treatment, in only about one-quarter of the post-traumatic cases does this same interval obtain. Instead, the peak period for initial seizures in these latter cases lies within the first 6 months.[46,48]

(b) *Frequency of aspiration.* The possible influence of the frequency of aspiration can be examined in the same way—for it may be suggested on *a priori* grounds,[10,36,39] that the more rapidly the abscess is sterilised and evacuated the less marked will be the fibroglial reaction which its presence in the brain provokes.† To this end, the incidence of seizures in cases of brain abscess treated with daily aspiration and injection of antibiotics may be compared with that in cases in which the abscess was aspirated at longer and more irregular intervals.

Of the patients surviving after treatment, 39 per cent had been treated in the former manner and 42 per cent in the latter. The incidence of seizures (after recovery from the illness) in the group treated with frequent aspirations and injections is 43 per cent; while the incidence in patients with less frequent puncture of the abscess is 53 per cent. While the statistical significance of this difference of 10 per cent is doubtful in this relatively small group of cases,‡ it may indicate that frequent puncture of a cerebral abscess (and frequent instillation of antibiotics) contributes something towards a diminution in the risk of seizures developing after treatment. It also may be of interest to note that of 7 of the earlier cases in this series in which intracerebral abscesses were treated by continuous drainage through tubes, seizures developed in 5; whereas this occurred in only 1 of the 5 cases of subdural abscesses treated in this way.

(c) *Instillation of radio-opaque material.* Two other aspects of surgical treatment of an intracerebral abscess are also sometimes indicted as epileptogenic, although our experience suggests that neither of them contributes significantly to the risk of development of seizures after recovery from a brain abscess.

The first of these is the use of radio-opaque materials[19,24,25,28,40,41,52,54,55,56]

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* It may be significant in this respect that repetition of leucotomy operations, presumably leading to more extensive glial reactions in the brain, raises the seizure incidence to about 47 per cent.[13,14]

† On the other hand, data referred to earlier (*vid. sup.*)—particularly in relation to head injuries[46]—do not indict infection *per se* as the critical epileptogenic factor, as far as late seizures are concerned.

‡ The probability of such a difference being ascribable to chance is 1 in 3.

(usually Thorotrast or Pyelosil) which, in numbers of clinics including our own, are injected into the abscess to permit its radiological visualisation. These substances are gradually taken up by the cells proliferating at the margin of the abscess during the process of capsule formation,[10,16,56] and a small fraction passes into the neighbouring tissue fluids in the brain and thence into the general circulation. There is no statistically reliable evidence —in our own, nor in other series of cases[24,56]—that the use of these substances predisposes *per se* to the later development of seizures. Moreover, it might be added that the presence of such materials within a loculus in an abscess does not (as has sometimes been suggested[10,52,56]) influence the rate of capsule formation around that loculus—for we find that encapsulation appears to proceed with equal speeds and to equal degrees in opaque and non-opaque loculi of similar age, as evidenced by histological examination of the abscess after removal at operation or autopsy.

(d) *Instillation of antibiotics.* A second factor is the use of antibiotics, which are injected into the evacuated abscess cavity or cavities at each aspiration, as an integral part of treatment. Because such antibiotics, when in direct contact with brain tissue in adequate concentration, are more or less active convulsant agents,[44,58,59,63] it has been suggested that their use might provoke seizures during, and even after surgical treatment of brain abscesses.

Certainly it is true that after their introduction into an abscess cavity these substances diffuse out into the surrounding tissue fluid and into the circulation; but the local concentrations resulting therefrom never approximate to the known convulsive concentrations of these substances.[59,63] The only situation in which a convulsive concentration of antibiotics might be released in the brain in this way is when the abscess communicates with a ventricle, so that material injected into it passes immediately into the ventricular system—but even then, the antibiotic solution is diluted with cerebrospinal fluid. Nevertheless, intraventricular rupture of an abscess sometimes produces generalised seizures as an immediate consequence, for this and other reasons; but we have no evidence that even this predisposes to the subsequent development of seizures, should the patient be sufficiently fortunate to survive such a disaster.

ELECTROENCEPHALOGRAPHIC STUDIES

An evacuated, healing cerebral abscess is gradually replaced by a dense fibroglial cicatrix, the histological features of which are essentially similar to those of a post-traumatic brain scar.[37–39,51] At the borders of this proliferating glial tissue (developing outside the original capsule of the abscess) an abnormal vascular pattern is gradually established. This results partly from initial thromboses in small vessels in the acute stages of the infection, and partly from later extracapsular reactions to the gradual obliteration of surrounding capillaries by the developing fibroglial tissue. As a result, at the borders of the replacement scar there are varying numbers of surviving neurones whose blood supply is diminished, and whose metabolism is disordered

in consequence.[37,39] It is reasonable, on the basis of what is known concerning the activity of such neurones in relation to post-traumatic scars,[34,39,65] to suggest that the activity of these abnormal cells might bear some relation to the production of seizures following recovery from a brain abscess.

Analysis of the pathological significance of this last factor is facilitated by electroencephalographic studies before, during and after surgical treatment of cerebral abscesses, supplemented by direct cortical recordings in appropriate cases. In the present series, 70 such recordings were made on 30 of the surviving patients; and these studies revealed two principal types of paroxysmal electrical disorders, additional to other electrical abnormalities.

(a) First there are *bilaterally synchronous paroxysmal discharges*, the cerebral distribution of which is relatively independent of the site of the original abscess in that the discharges appear at maximum amplitude in both frontotemporal areas. Such disorders may appear transiently during and immediately after treatment, disappearing sooner or later; or they may (in a few cases) develop early in the story and persist more or less indefinitely (*q.v.*). They have been observed in one-tenth of our cases studied in this way. Clinically, the seizures accompanying such discharges are usually generalised convulsions, and generally respond to anticonvulsant medication. We believe that this phenomenon represents the activation, by the general systemic effects of the infection, of an inherent convulsive predisposition; for such a proclivity is displayed electrically by about one-tenth of the population at large.[65] Similar results may occur in such patients with any infection, whether or not it specifically involves the nervous system.

(b) In addition, but more often without these abnormalities, *focal paroxysmal discharges* may be fired from neurones at the borders of the abscess, and later of its replacement scar. These discharges appear first as localised paroxysmal slow waves (whose frequency is 3 c./sec. or less) in the immediate vicinity of the abscess, especially when the capsule is beginning to form. They increase in amplitude and decrease in frequency as the tension within the abscess rises (a change of which they provide a sensitive index), and diminish when its contents are evacuated, at the same time becoming less widespread.

After sterilisation and evacuation of the abscess their frequency accelerates, and continues to increase gradually as extracapsular fibroglial proliferation develops, so that eventually bursts of waves at 6 c./sec. or trains of fast spikes may be fired from collections of neurones at the periphery of the now established cicatrix. This type of abnormality, present in one-third to one-half of our cases at various postoperative intervals, may be associated (sooner or later) with focal seizure phenomena occurring either alone or as a prelude to generalised seizures. It is more difficult to alleviate this type of disturbance with anticonvulsant medication than the previous abnormalities; and it is important to note that this type of localised seizure discharge is potentiated by barbiturates, administration of which may in fact be used to unmask them during electroencephalographic examination.

It is also significant to note that the relative incidence of these two types

of abnormality changes with increasing intervals of time after successful surgical treatment of an intracerebral abscess. Localised paroxysmal discharges were present in one-third of our cases within the first 3 postoperative months, whereas between 6 months and 1 year this type of abnormality was seen in about half the cases. On the other hand, the incidence of bilaterally synchronous paroxysmal disorders was greatest within the first 3 months following treatment, after which they usually disappeared rapidly, particularly in those cases in which anticonvulsant medication was given. These findings suggest that the former type of abnormality is dependent on the progressive development of extracapsular fibroglial reactions, whereas the latter is not.

CONCLUSIONS

The principal findings emerging from this study, and their implications for the surgical treatment of cerebral abscesses, may be summarised as follows.

1. Seizures, of some type or another, constitute the principal morbid result of intracerebral abscesses, occurring in almost half of the surviving patients. This incidence is more than twice that following subdural abscesses.

2. Frontal abscesses carry the greatest risk of development of seizures in surviving patients, followed by parietal, temporal and occipital abscesses in that order. The general nature of the seizures, as well as their specific manifestations, also varies with the location of the abscess.

3. The nature of the infecting organism, its mode of entry into the brain, and the instillation of antibiotics and radio-opaque materials into the abscess during treatment do not influence the risk of subsequent development of seizures.

4. The development of seizures after recovery from an intracerebral abscess does not depend on the occurrence of seizures earlier in life, nor upon their development during the acute stages of the infection or during its treatment.

5. Institution of surgical treatment after a lapse of 3 weeks from the first indications of the presence of an intracerebral abscess carries one-third of the risk of late seizures implied by treatment at an earlier date.

6. The risk of late seizures is possibly a little less with frequent aspiration of the abscess (and instillation of antibiotics) than with less frequent treatment.

7. Some three-quarters of the patients with post-abscess seizures display the first ictal phenomena between 6 months and 1 year after completion of surgical treatment.

8. Clinical and electroencephalographic evidence suggests that most of the late seizures arise as a result of abnormal discharges from neurones in the vicinity of the fibroglial cicatrix which eventually replaces and surrounds the evacuated, sterilised abscess.

9. It appears that these abnormalities are provoked, not by the processes of initial capsule formation, but by the extracapsular fibroglial reactions

which proceed in the brain for some 6 months after healing of the original lesion.

There are two practical implications which arise from these findings. First, all patients with intracerebral abscess should be subjected to frequent postoperative electroencephalographic studies during the first year of recovery, particularly during the first 6 months. Second, patients in whom localised paroxysmal discharges develop during this period should be subjected to excision of the healing cicatrix and the surrounding fibroglial tissue under electrocorticographic control, if they have seizures that are disabling in spite of adequate anticonvulsant medication. The use of electrocorticography is essential, because mere excision of the directly visible replacement scar does not remove the source of abnormal neuronal activity which is eventually expressed as seizures.

Finally, we would suggest that there is now an urgent need for an experimental pathological study of the *late* reactions of the brain to healing of an intracerebral abscess; for there is as yet no direct information on this point, as there is with penetrating injuries of the brain.[37–39,50]

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ISOTOPE ENCEPHALOMETRY

A REVIEW OF SOME BASIC DATA*

LYLE A. FRENCH, M.D., AND SHELLEY N. CHOU, M.D.
Department of Surgery, Division of Neurosurgery, University of Minnesota Medical School, Minneapolis, Minnesota

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THIS report was originally presented as an introduction for a panel discussion on the use of radioisotopes in the investigation of brain tumors. It concerns some of the basic physical data attendant with the problem of radioisotope encephalometry and includes a review of some of our experiences with this technique.

Radioactivity is a physical phenomenon arising from a disturbance in the stability of an atomic nucleus. Under normal circumstances an atom is an electrically balanced structure composed of a nucleus with a positive charge and orbital electrons with negative charges. The nucleus has relatively great mass, being composed of protons and neutrons whereas the orbital electrons have practically no mass. However, a neutral atom is not a static structure composed of particles in a fixed position but rather it is a dynamic system. In the nucleus the protons and neutrons do not maintain fixed arrangements but mill around one another in a state of agitation; moreover, the protons and neutrons should not be considered as two different particles, one permanently positive and the other permanently neutral, but theoretically as being interchangeable in their status. For example, a neutron may become a proton by emission of an electron, or negative β particle, or contrariwise a proton may convert to a neutron by emission of a positive β particle (a positron). The forces that hold the constituents of an atomic nucleus together are in part electrical and in part mechanical cohesive forces. When an atomic nucleus has just the right proportion of particles in the two different states (protons and neutrons) the energy involved in dynamic transformation of one into the other is balanced. But occasionally this ratio is unbalanced. When this occurs, as it does especially in elements with atomic weights over 209 or in other elements artificially rendered radioactive, the unstable atom disintegrates, ejecting from the nucleus either an α or a β particle. This is not a complete destruction of the atom. It is simply the expulsion of a small particle from the nucleus, whose other components then rearrange themselves and settle down to be (either temporarily or permanently) a stable atom of another element. In naturally radioactive substances there are two, and only two, types of disintegration. In one a particle is expelled which is identical with the nucleus of a helium atom. This is an α

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particle and consists of two protons and two neutrons. It is positively charged, is heavy, moves slowly, and has poor penetration. The other type is β disintegration or decay. A β particle is an electron. It usually has a negative charge, has practically no mass, and although its penetrating powers are greater than α particles it penetrates only from 0.5 mm. to 1.0 cm. in biological tissue. Occasionally the emitted β particle has a positive charge and, as stated above, is then called a positron.

Gamma rays, which are electromagnetic in nature, may be emitted in the course of either of these types of disintegration. They may come from the nucleus, in which case they represent excess nuclear energy, or they may come from the inner electron orbits of the radioactive atom. A special type of gamma radiation arises when a positron emitted from the nucleus of an atom collides with an electron. This results in annihilation of the particles and the release of two quanta of energy that are given off at a 180-degree angle to one another or, as Sweet *et al.*[6] have so aptly termed it, back to back. Gamma radiation, which is energy, rather than particulate matter, travels rapidly, penetrates well, and is identical to x-rays, light rays, etc. It is these that are detected in isotope encephalometry as done today.

During the early stage of development of isotope encephalometry Geiger-Mueller tubes were used to pick up radiation. The principle of the Geiger-Mueller tube is the interaction of radioactive particles with molecules of gas which results in ionization of the gas. These ions move toward the positively charged wire electrodes. A current flow is produced which generates a pulse of voltage that is subsequently electronically counted. Since the detection substance is a gas, very few of the gamma radiations strike a gas molecule because the density of the gas is low. An average G.M. tube detects only 1 to 2 per cent of γ radiation.

Scintillation counters have proved more efficient, for here the detecting substance is a solid crystal. As many as 60 per cent of γ radiations are detected. The mechanism of a scintillation counter is based on the striking of a solid crystal by the radiation. This results in production of a minute flash of light. Materials that emit flashes of light under high energy bombardment are called phosphors (crystallized NaI, Ca tungstate). The flash of light travels to the photocathode of a phototube and produces photoelectrons. These negative electrons are attracted to a positive charged anode, so a current flow is established which in turn generates a pulse of voltage which can be counted. Scintillation tubes are now used quite universally for isotope encephalometry because of their greater efficiency.

The accuracy of isotope encephalometry has improved with the use of scintillation counters because the higher the number of counts per unit time the greater the statistical significance. Also higher counts per unit time have permitted more confining shielding of the counting tube (or collimation), for this governs the delineation of a pattern. A wide open, or poorly collimated, tube permits a high counting rate but the tube "sees" a wide area so the directional quality or accuracy of localization is lost. A partially collimated

tube produces lower counts but increases the definition of the pattern. For the past several years we have used a partly collimated scintillation counter, one that covers an angle of 15 degrees from the crystal. Occasionally a preliminary scan is made with a poorly collimated tube and this is followed by a second survey using a tube of better directional characteristics.

The fundamental principle upon which isotope encephalometry is based is the relative concentration of these radioactive substances in pathologic compared to normal brain tissue.

The concentrating materials generally used have been:

1) *Diiodofluorescein labeled with I-131* (DIF).—This is a γ emitter that concentrates up to 1–10 in tumor tissue. This was the first substance used for isotope encephalometry. It has been replaced by others for various reasons, one of which is its rapid drop in blood and tissue levels. One hour after intravenous injection the blood stream radioactivity drops approximately 50 per cent of the initial level. Therefore counting must be started within 1 hour after injection and counting must be done of symmetrical positions on each side as the head survey progresses because there is a significant drop in the counting rate during the period required for a complete survey. Repeat examinations or rechecks of suspicious areas must be done immediately and even then are less accurate because of lower counting rates. In our hands at the University of Minnesota approximately 65 per cent of intracranial tumors could be localized using this technique.[3]

2) *Radioactive iodinated human serum albumin* (RIHSA).—This is a γ emitting substance and has I-131, as does DIF, as its radioactive substance. RIHSA gives sustained and stabile blood and tissue levels; 24 hours after intravenous injection, approximately 60 per cent of the original level is present. The technique used by us was to make our first counts 24 hours after injection. Repeat counts were made in the next 24 to 48 hours, for during this time the counting rates drop very slowly. In fact, occasionally the differential uptake between brain and tumor even increased in the later counts. One disadvantage of RIHSA is that it is gradually metabolized, liberating free I-131 which is taken up by the thyroid unless the gland is previously blocked by stabile iodine, namely, Lugol's solution.

In our earlier attempts at isotope encephalometry we depended upon finding a difference in counts in symmetrical positions on each side of the head. A difference of 10 per cent or more was considered significant if it persisted on rechecking these positions. Using this technique with RIHSA and scintillation counters, our accuracy in localizing brain tumors was 68 per cent.[2] If clinical data were used the per cent correct localization was approximately 95 per cent.[3] However, it is felt that the use of supplementary clinical data excludes a true evaluation of the technique.

It was felt, also, that some method of analysis other than asymmetry might improve the accuracy of localization. Midline lesions could not be detected by asymmetry and cystic lesions which took up less radioactive material than normal brain tissue would tend to give a false diagnosis of a focus

on the wrong side. Therefore a graphic method of analysis was developed.[1] This method relates a position counted with all positions and also with a "normal" counting rate for that position. In this way an area which on routine counting did not show a 10 per cent difference in counting rates, and was therefore called normal, could be plotted on a graph and might be abnormal depending upon the shape or slope of its curve.

Fig. 1 shows the "normal" curve determined by plotting the average counts for each of the 12 established positions. It also shows the curve ob-

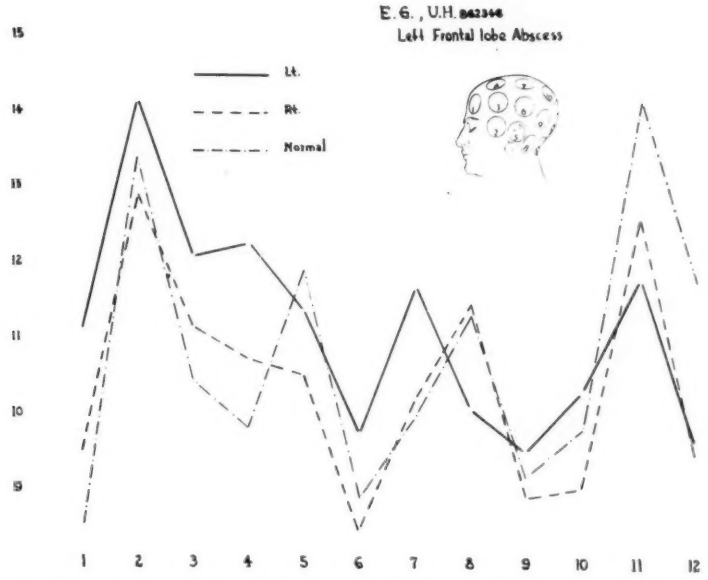

FIG. 1. Graphic analysis method of localization of brain abscess of left frontal lobe. There is some elevation of isotope activity in frontal region on both sides, but the predominance is on the left.

tained on the right and left sides of a patient with a left frontal abscess. The location of the lesion is apparent.

During the past year 69 patients were given RIHSA and counts were made with a scintillation counter. The data were analyzed by both asymmetry and the graphic method. Results are given in Table 1. Both were analyzed without clinical or other laboratory data.

3) *Phosphorus*^{32} (P^{32}).—This β particle emitter has been used extensively by Selverstone *et al.*[4] to help locate tumors at the time of surgery. It concentrates well in tumor tissue but because of its poor penetrating powers it does not penetrate the calvarium, or even the dura mater, so cannot be used for external encephalometry.

4) *Positron emitting substances.*—The first use of positron emitting substances for isotope encephalometry was by Sweet[5] and Wrenn *et al.*[7] in 1951.

Because of the paired γ radiation emitted when the positron undergoes annihilation it has been possible to use paired scintillation counters placed on each side of the head and connected with a coincidence counting system. This has permitted greatly improved resolution or definition of the source of radiation. Accuracy of 75 per cent for brain tumor detection and 83 per cent for brain abscesses has been obtained.

The apparatus we now use for detection of positron emitting isotopes is a scanning device that can be used with or without coincidence counting circuits. The scanner works not only from a sagittal but also from a coronal plane. Our phantom studies were done with Na^{22}, Co^{57-58}, As^{74}, and Fe^{55}. Because of the high cost of As^{74}, we usually have used Na^{22} as the positron emitting substance, but the differential concentration of this substance has not been sufficient to warrant optimism with its use. It is believed that As^{74} will soon be available at a much lower cost.

TABLE 1

Comparison of results of isotope encephalometry using techniques of asymmetry and graphic analysis

	By Asymmetry	By Graphic Method
Tumors correctly localized	17 (68%)	21 (84%)
Tumors not correctly localized	8 (32%)	4 (16%)
Other space-displacing lesions correct	5 (71%)	7 (100%)
Other space-displacing lesions incorrect	2 (29%)	0
No lesion and no focus localized	36	36
No lesion but false focus	1	1
Total	69	69

We anticipate in the very near future having an anticoincidence counter functioning along with the regular coincidence setup. The principle of this is to decrease the background activity so that better delineation of a focus may be obtained. It should help solve the problem of too little sensitivity or too small concentration of isotopes for the visual record to indicate tumor location clearly. Phantom studies have shown that to be detected the minimum tumor size must be 40 cc. by volume and contain 3 times the amount of radioactivity as the surrounding tissue. It may, of course, be smaller with more concentration of isotope.

In conclusion it is felt these techniques have not been exhausted and further work is necessary. An accuracy of 65 per cent to 75 per cent for localization of brain tumors can now be obtained routinely.

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ORIGIN, SPREAD AND NEUROSURGICAL TREATMENT OF THE PSYCHOMOTOR TYPE OF SEIZURE DISCHARGE*

JOHN F. KENDRICK, M.D.†, AND FREDERIC A. GIBBS, M.D.‡
Neurosurgical Unit, Manteno State Hospital, Manteno, Illinois§

(Received for publication August 25, 1956)

PSYCHOMOTOR epilepsy has been defined as a condition characterized clinically by trance-like attacks and confusional episodes[13] and electroencephalographically by spike discharges which (with scalp recordings) appear to be focal in the anterior temporal region.[9,10,12] Convulsions occur in a high percentage of such patients, and personality disturbances and psychosis are common.[11,12]

In some severe cases of psychomotor epilepsy in which the patient does not respond to medical treatment, unilateral removal of the anterior third of the temporal lobe produces a good therapeutic result.[3,4,14–16] When the focus is unilateral and a unilateral operation is performed, more than 50 per cent of patients are rendered seizure-free.[4] However, only 1 out of 4 patients with independent bitemporal foci is freed of seizures by a unilateral operation. The number of cases in which bitemporal lobectomies have been performed for bilateral psychomotor epilepsy is too small to permit evaluation; in 1 case reported by Terzian and Dalle Ore[36] extensive bitemporal resection produced serious personality changes and disturbances in behavior.

Removal of the anterior third of the temporal lobe does not always eliminate the spike discharges and the postoperative tracing may reveal spikes of the same general type as were present preoperatively. More commonly the spikes are reduced in voltage and have an altered wave-form with a strong positive component (preoperatively, they had a strong negative component). In such cases one is led to wonder whether the surgical attack was misdirected or was not sufficiently radical. The therapeutic result is in general inversely proportional to the amount of residual electroencephalographic "seizure" activity. The present study was undertaken in the belief that if the origin and spread of the psychomotor discharge could be accurately determined, the effectiveness of neurosurgical treatment could be increased.

In the hope of obtaining comparable data on a group which would be in contrast with the psychomotor epileptic group, plans were made to obtain

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† Richmond Memorial Hospital, Richmond, Virginia.

‡ University of Illinois, College of Medicine, Chicago, Illinois.

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observations on a group of schizophrenics who were referred for frontal lobotomy. This latter group turned out to be not so much contrasting as similar. For valid control studies on the electrical activity in the depths of the brain, patients will have to be studied with no evidence of cerebral disorder. The most favorable group for such studies would be patients referred for frontal lobotomy because of intractable pain. Heath *et al.*[37] have reported some preliminary studies of this type.

TEMPORAL LOBE FUNCTION—LOWER ANIMALS AND MAN

Animal studies have revealed functional connections between the temporal lobe and almost all parts of the cortex, the basal ganglia, the thalamus and the reticular formation of the brain stem,[1,2,5,6,23,25,31,33–35] and have shown that the mesial and anterior temporal areas are part of the limbic system. The implications of this new information for neurosurgery were discussed by MacLean[23] in an excellent review published in this *Journal*. Most of the anatomicophysiological studies on the temporal lobe have been done on animals and it is not safe to assume that these are completely applicable to man, but Kaada and his co-workers[18] have shown that seizures which resemble the psychomotor seizures of man are produced in cats by stimulation of the amygdaloid region. The spread of seizure discharges to and from the temporal lobe of the monkey has been studied in detail by Faeth, Walker and Andy.[7]

In 1938 Klüver and Bucy[21] described the marked changes in behavior that occur in the rhesus monkey with radical bilateral temporal ablations. The Klüver-Bucy monkeys showed psychic blindness of an agnostic type, hypermetamorphosis (constant shifting of attention), emotional changes (tameness, loss of fear, loss of rage, etc.), changes in dietary habit and increased sexual activity. These extreme disturbances of behavior do not occur with either unilateral temporal lobectomy or limited bilateral anterior temporal lobectomy in man,[3,4,11,14–16] but comparable disturbances have been reported by Terzian and Dalle Ore[36] and Petit-Dutaillis *et al.*[30] in cases of bitemporal lobectomy.

Heath *et al.*[37] have observed epileptiform discharges in the depths of the frontal lobes in the "septal" region and also to a lesser extent in the hippocampus of patients with psychosis unassociated with epilepsy. As will be reported in a later part of this paper, we obtained spike discharges from the depths of the brains of schizophrenic patients, and these discharges were indistinguishable from those seen in epileptics. Elucidation of these findings and determination of the site of the discharge in psychotics were added to the problem of delimiting the psychomotor focus because it was felt that a comparison of findings in epileptics with psychosis and in patients with psychosis (but without epilepsy) diagnosed *schizophrenia* might be informative and might lead to a more rational surgery for the treatment of both psychomotor epilepsy and psychosis.

MATERIAL AND METHOD

Seventy-five patients, who had been psychotic for a period of 5 to 20 years, were included in this study. Thirteen had psychomotor epilepsy and psychosis; 62 were classified as psychotic without epilepsy and were referred for psychosurgery because of prolonged, severe psychiatric disorder usually with assaultive behavior that had not responded to medication, various types of shock treatment or any other available therapy. No surgical procedure was employed in these cases without first obtaining written consent, after careful explanation, from responsible relatives or guardians.

In all cases several presurgical electroencephalographic recordings were made from the unopened skull with scalp electrodes. At surgery electrodes were placed on the exposed cortex and multiple needle electrodes were inserted into the depths of the brain. Postsurgically scalp recordings were repeated at intervals to determine whether abnormalities that were present before surgery had been eliminated and/or new abnormalities had been produced.

Scalp electrodes were placed over both hemispheres in the frontal, parietal, temporal, anterior temporal and occipital regions. Also in many cases nasopharyngeal recordings were made with electrodes of the type described by MacLean.[22] Recording was monopolar; the most usual common reference was one or both ear lobes but the mid-occipital and mid-parietal regions were often used and sometimes recordings were made with a reference electrode on the chin or nasion. In most cases a recording was obtained with the patient awake, asleep and under Pentothal anesthesia. Often abnormality appeared during sleep which was not evident in the waking state. Some patients who had normal recordings when awake and in spontaneous sleep, showed definite abnormalities under Pentothal anesthesia. The chief reason for preoperative studies under Pentothal anesthesia was to ascertain, if possible, whether seizure discharges would appear during a surgical level of Pentothal anesthesia; previous experience has shown that such anesthesia usually reveals the same focal seizure discharges as appear in normal sleep.[8,9] This gives some assurance that spike discharges that do not appear in the waking state are not sleep or anesthesia "artifacts." Further assurance on this point is obtained from the following: Spike seizure discharges (exclusive of small sharp spikes) almost never occur in the anterior temporal region during sleep in nonepileptic and nonpsychotic persons. In those cases in which the spike discharge shows only with Pentothal anesthesia it occurs in the same general region as it does in other cases. Studies were carried out to determine whether control subjects, who do not have a history of epilepsy and without electroencephalographic abnormalities, show spike seizure discharges when anesthetized for general surgery with Pentothal.[20] These studies lead to the conclusion that occasional spike-like patterns appear in normal persons during deep Pentothal anesthesia but these are distinguishable from spike-seizure discharges.

In order to obtain the maximum amount of information in the shortest possible time during surgery and also in order to provide as complete and

precise a view as possible of the discharging area, recordings were made simultaneously from many points on the surface of the scalp, from the surface of the brain and from the depths of the brain. This was accomplished by employing in the operating room four 8-channel Grass electroencephalographs. These, when connected to electrodes on the patient's head and in his brain, provided 32 simultaneous tracings.

Scalp recordings during surgery were sometimes made from the usual type of solder disc electrodes that were used for preoperative recordings, but in most cases hypodermic needles were employed as scalp electrodes at operation. For recordings from the exposed surface of the brain, wick electrodes in a Grass electrode holder were employed and also postage-stamp electrodes of the type described by Henry[17] and spatula-type electrodes as described by Marshall.[26]

The depths of the brain were explored with 4 to 8 Grass multi-electrode needles.[12] Each of these needles provides 10 electrodes situated 1 cm. apart along the shaft, which is 3 mm. in diameter and rounded at the tip. The depths of the insertion and number of recording electrodes depended on the area of brain being explored. Some of these needles were equipped with ports at each ring, permitting injection at any desired point of a convulsant or anesthetic drug or some other pharmacological agent. By this means strychnine, Nembutal and other substances were injected in order to create an artificial focus of seizure activity or to suppress existing seizure activity. The results of the strychnine studies are reported in detail in another article.[19] Electrical stimuli were applied in some cases to the surface and depths of the brain through the same electrodes that were used for recording. The source of the electrical stimulation was a Grass stimulator; usually the stimulus was a 60-cycle square wave, alternating current.

Before the needles were placed in position, air was injected into the ventricles by means of a rubber catheter which was inserted into the ventricular system through a posterior temporoparietal burr hole. In order to obtain better visualization of the temporal horns the catheter was directed, whenever possible, into the temporal horn of one or both ventricles. The radiographs were made with a specially constructed 200 mamp. portable X-ray instrument.* A cassette holder was attached directly to the operating table for anteroposterior and lateral roentgenograms with the head in an anteroposterior face-up position.

Insertion of the needle electrodes through burr holes or through the craniotomy opening was accomplished *without* the aid of stereotactic instrument; the needles were inserted free-hand and aimed at what was believed to be the location of the deep structures from which recordings were desired. The correctness of the insertion was checked by noting the position of the needle on ventriculographic studies.

Almost all of the surgical recordings were carried out with the patient

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* This was especially designed and built by the Schick X-Ray Company, Chicago, Illinois with funds granted to the University of Illinois by the Rockefeller Foundation.

under Pentothal anesthesia. However, a few were done under local anesthesia.

The particular surgical procedure that was employed in a given case was determined by the type and severity of the patient's illness and by the focal abnormalities encountered in that case. The objective was to remove the discharging areas as completely as possible and block the major pathways of spread; excisions varied from unilateral partial frontal lobe section to bilateral frontal lobe section and bilateral anterior temporal lobectomy. The number and type of operations are shown in Table 1. Immediately after the surgical exposure had been completed, depth and surface recordings

TABLE 1

Operative procedures in 75 cases of psychomotor epilepsy and/or psychosis

88 operations
- 72 temporal lobe excisions
  - 24 patients with bitemporal lobe excisions
  - 24 patients with unitemporal lobe excision
- 33 biorbital prefrontal lobotomies
- 15 unilateral orbital prefrontal lobotomies
- 10 bimedial prefrontal lobotomies
- 5 unilateral medial prefrontal lobotomies
- 3 bilateral prefrontal lobotomies (all four quadrants)
- 4 unilateral prefrontal lobotomies (all four quadrants)
- 17 patients with biorbital prefrontal lobotomies and bilateral anterior temporal lobectomies

were made. When the operation was in two stages, repeated scalp recordings and clinical studies were made between procedures. The patients were followed with serial postoperative electroencephalograms and continuing clinical evaluations.

RESULTS

Waking and sleep recordings from the scalp revealed anterior temporal, temporal and frontal spiking in all 13 of the frank epileptics and in 13 who were classified only as schizophrenic. The Pentothal studies added similar findings in 15 more of the group of psychotics without epilepsy. Thus, 41 of the 75 patients showed spiking in the scalp recordings. On the other hand, 74 out of the 75 had spiking in the depths of the frontal and/or temporal lobes at the time of operation.

In some cases very high voltage seizure activity occurred in the mesial surface of the temporal lobe and in the mesial orbital cortex of the frontal lobe without manifesting itself in anything that could be reliably interpreted as a spike in scalp recordings. Fig. 1 demonstrates roentgenograms and Figs. 2, 3, 4, and 5 some scalp and depth recordings showing spiking in the depths with and without scalp concomitants. From this it appears that the failure to see spike discharges in routine electroencephalography is no guar-

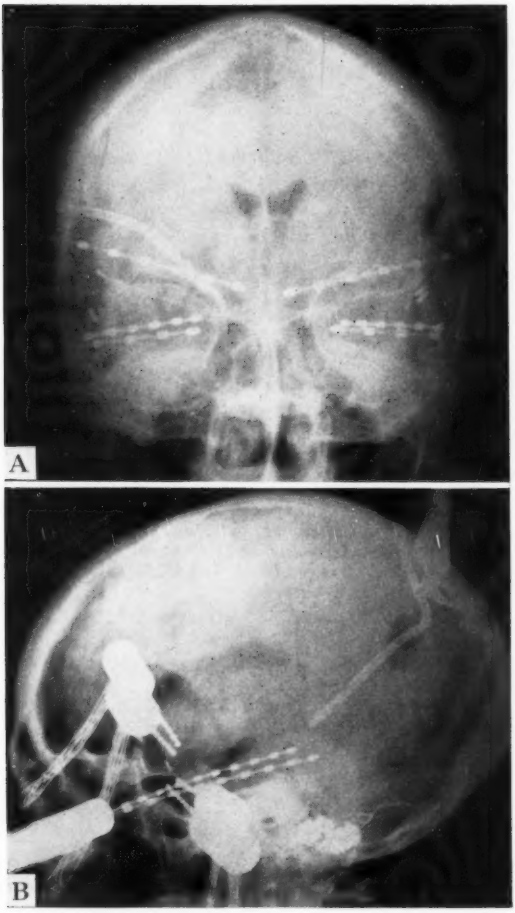

FIG. 1. (A) Anteroposterior ventriculogram showing 6 needle electrodes in position. The two superior needles are in posterior frontal-orbital regions. The lower 4 needles are in the temporal lobes. Separate recording electrodes are spaced 1 cm. apart along each needle. (B) Lateral view (same patient and electrode locations as in A). The most inferior pair of needles extend into the anterior temporal lobes. The other temporal pair extend from the lateral anterior temporal lobes posteromesially into the hippocampal areas. The superior pair extend into the posterior frontal-orbital regions.

antee that seizure activity of the highest possible voltage is not occurring in a deep structure.

An unexpected complication that is encountered in the surgical attack on epileptic discharges in the anterior temporal lobe is the following: Spike discharges that are clearly evident in the recording made in the waking state, during spontaneous sleep, and also during Pentothal anesthesia before the skull is opened, often disappear when a burr hole is made and may be non-

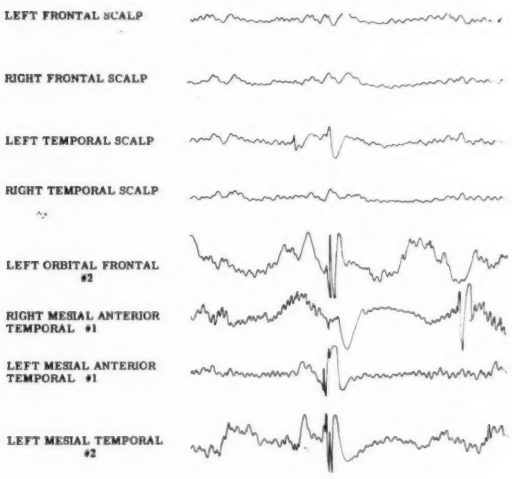

FIG. 2. Spike seizure discharge in left orbital-frontal and left mesial temporal regions with concomitant spike showing in the left temporal scalp recording, but not in the frontal scalp recordings. Immediately following is a spike discharge confined to the right mesial anterior temporal area (uncal) and without spread to other areas.

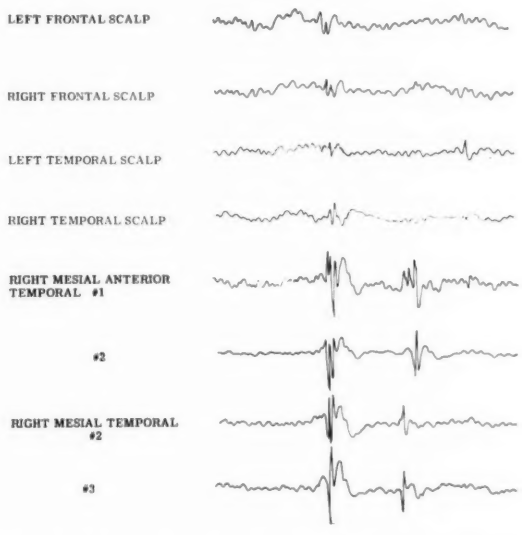

FIG. 3. Temporal spiked discharge (uncal and hippocampal) showing minimally in frontal and temporal scalp leads bilaterally. Immediately following there are independent spike discharges in the right mesial temporal and the right mesial anterior temporal areas which are not evident in scalp recordings.

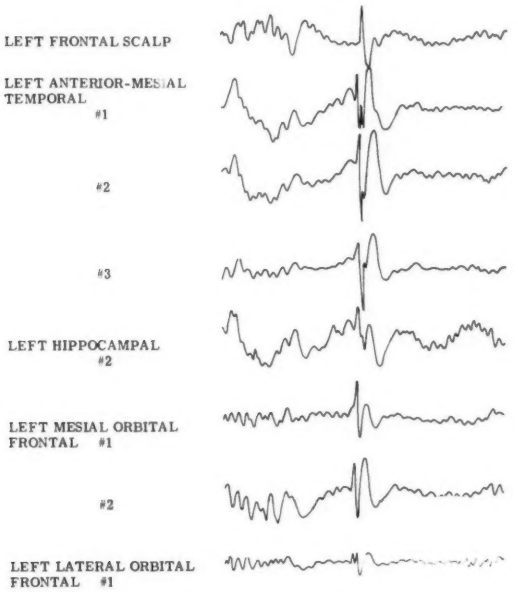

FIG. 4. Spike discharge in the left anterior mesial temporal (uncal) region with spread to the left mesial orbital-frontal area and showing also in the left frontal scalp recording.

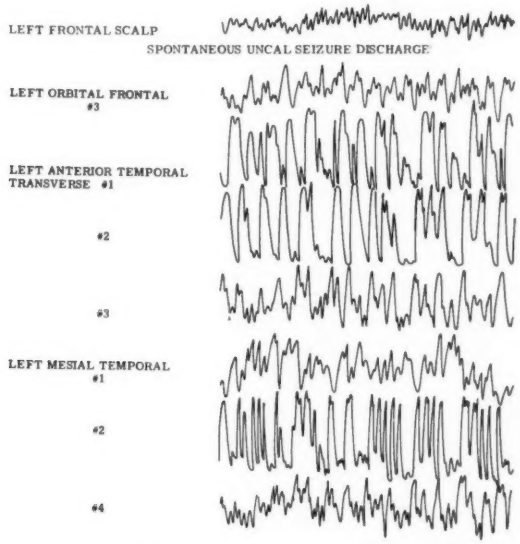

FIG. 5. Spontaneous discharge in the left uncal region with hippocampal involvement (left mesial temporal #2) and slight spread to left orbital-frontal region with only questionable evidence of discharge in the left frontal scalp recording.

evident in either scalp recordings or recordings from the lateral surface of the temporal lobe, but usually this occurs only on the operated side. In cases of bilateral anterior temporal spikes in which the decision was made to operate on the side showing the highest voltage and the most consistent spike activity preoperatively, it was our experience that the simple procedure of making a regional burr hole or turning a flap at times reduced the amount of spike activity on the operated side so much that it appeared to be the side of the minor focus. Spike activity in the lateral anterior temporal region may be reduced by 1) opening the overlying skull, 2) exposing the temporal lobe, and 3) needling the temporal lobe. Our experience with the mesial surface of the temporal lobe indicates that here the situation is reversed, i.e., exposure or needling and mechanical stimulation tend to increase and may even initiate seizure activity from this region.

Some doubt may be felt as to the reliability with which one can distinguish between spontaneous seizure activity and seizure discharges initiated by mechanical stimulation. Such concern is justified, but the experienced investigator soon comes to realize that discharges caused by mechanical irritation flare up acutely and tend to subside. The spontaneous discharge, on the other hand, can be seen from a distance and when approached from different angles it is found to have a definite site and a fixed pattern.

Multiple independent foci in the temporal lobe were common in these patients with psychomotor epilepsy. The mesial orbital surface of the frontal lobe was frequently found to be the site for independent focal spike discharges. In the present series of psychomotor epileptics operative recordings revealed that the mesial surface of the temporal lobe was the commonest site of focal discharging (Fig. 6). A focus of spike activity in the thalamus

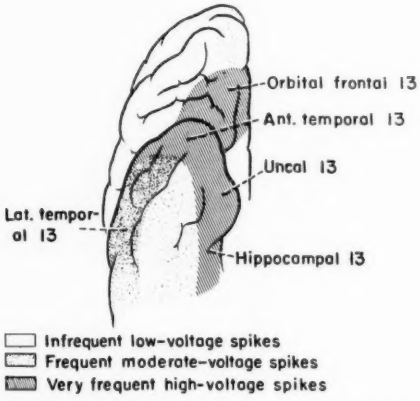

FIG. 6. Site of spiking in psychomotor epileptics with psychosis (13 patients). Intensity of spiking is indicated by stippling and crosshatching.

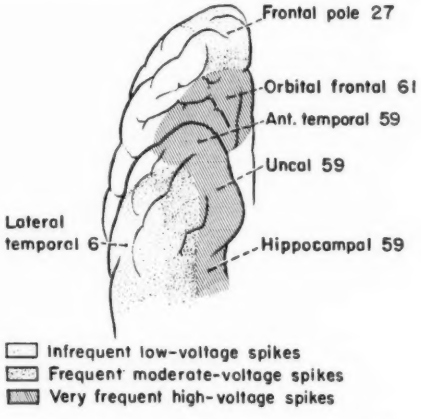

FIG. 7. Site of spiking in psychotic patients without known epileptic seizures (62 patients). Intensity of spiking is indicated by stippling and crosshatching.

or basal ganglia was not encountered in this series, and our experience with strychnine and electrical stimulation suggests that the thalamus is relatively insensitive compared to the temporal and frontal lobes, and has a much higher threshold for epileptic discharges than the temporal and frontal lobes.

We had expected to use patients referred for lobotomy with a diagnosis of schizophrenia as a contrasting group to the psychomotor epileptics, but this was impossible because in a high percentage of these latter patients the preoperative electroencephalograms showed spike-like patterns, and in almost 50 per cent of cases a clearly defined spike focus in the anterior temporal region and/or in the frontal areas. The location of spike discharges as revealed at operation with surface and depth recordings in the psychotic group without clinical evidence of epilepsy is shown in Fig. 7. As will be seen in this group, the commonest site of an independent discharge is in the mesial orbital cortex of the frontal lobe with the mesial temporal lobe being almost as frequently involved.

A reciprocal spread of seizure discharges from the mesial temporal to the orbital frontal region was commonly seen in patients with psychomotor epilepsy, with or without psychosis, and also in patients classified as psychotic without epilepsy. Where secondary independent foci were present in either the orbital frontal or mesial temporal region many examples were seen of two-way spread and also of mass discharges of the entire mesial anterior temporal and orbital frontal regions.

Primary seizure discharges in the thalamus or basal ganglia were not found in the present series of cases. Seizure activity, either spontaneous or in some cases induced with strychnine, tended to spread from the mesial temporal to the anterior temporal and the mesial orbital frontal regions unilaterally and at times bilaterally. This seemed to constitute a system. Very high voltage discharges occur in the mesial temporal and mesial orbital frontal cortex without producing any reliable indication of their presence in scalp recordings.

Strychnine spike studies[19] carried out on 34 patients indicated a close functional interrelation between the mesial temporal and mesial orbital frontal cortex. Strychnine spikes and also spontaneous spikes spread freely between these areas but not to the rest of the brain. The anterior and a small portion of the anterolateral temporal lobe seemed to be part of the same "system," for they were commonly included in the area of spread from either the mesial temporal or posterior mesial orbital cortex. However, seizure activity in the lateral, mid-temporal and lateral frontal regions did not tend to spread to the mesial surfaces of either the temporal or frontal areas and the mid-temporal region seemed to be functionally isolated from the anterior and mesial surfaces. High voltage, repetitive discharges in the mesial surface of the temporal lobe were more likely to spread to the posteromesial surface of the temporal lobe and to the mesial orbital frontal lobe and thence to the opposite mesial orbital frontal and mesial temporal lobe before they spread to the lateral mid- and posterior temporal cortex.

In all of the 48 patients in whom temporal lobectomy was performed (72 temporal lobes removed) spike seizure activity was either markedly attenuated or absent after the operation. In no case was the seizure activity unmodified by the operation. In the cases in which spikes were still present they were of lower voltage and less frequent.

The mesial temporal and orbital frontal system is of great interest because it is commonly involved in patients who have severe psychiatric disorder. Our observations are in accord with those on the "septal" region published by Heath *et al.*[37] and with the work of Petersen *et al.*[29] They are in general accord with the observations of MacLean and Delgado[24] on monkeys and with the observations of Scoville *et al.*[32] on man.

THERAPEUTIC RESULTS

Only a preliminary report can be given of the therapeutic results in this group of 75 patients because the postoperative observation period is only 12 to 24 months. There were 88 operations and further surgical procedures may be considered on some of the unimproved patients. Of the total number of patients, 13 were frankly epileptic and psychotic, while the remaining 62 were classified as *schizophrenic without epilepsy*. All patients had had severe mental illness for at least 5 years and many for 10 to 20 years. To date, 31 patients (41 per cent) are at home or in mental condition to be at home if home care were available. Fifteen patients (20 per cent) are moderately improved, 11 (15 per cent) are slightly improved, and 13 (17 per cent) are unimproved. There were 5 deaths (7 per cent).

The results of excisions in the epileptics with psychosis were more difficult to evaluate than those in psychotics without clinical epilepsy. This is particularly true because the course of the seizures and the psychosis in patients with severe psychomotor epilepsy is often not parallel. The presence of mental deficiency before surgery and the fact that some of these patients have spent most of their lives in mental institutions must be taken into account in estimating the degree of benefit that might be achieved and in assessing the postoperative result. Of the 13 patients with severe psychomotor epilepsy, seizures have been absent since operation in 4 and greatly reduced with medication which was previously ineffective in the remaining 9. However, it must be emphasized that 8 of these patients have had only unilateral temporal operations, while all had bilateral (independent) temporal spikes electroencephalographically. Thus these patients may need multiple-stage operations with suitable time intervals for evaluation between procedures. It was largely in this group that the most disappointing complication occurred as a result of vascular deficits, produced in all probability during the course of extensive removal of temporal lobe from around the insula. Out of 72 temporal lobe excisions, hemiplegia occurred in 4 instances. The vascular loss was demonstrated in arteriograms as very poor contrast filling of the middle cerebral artery. However, the vascular insult may have also included the anterior choroidal artery. These particular patients were

thought to have been operated upon with the same caution as the others; care was taken to preserve the pial protection afforded anatomically to the Sylvian vessels and mesial temporal lobe. But apparently if the ablation of the mesial surface of the temporal lobe is carried back 6 or 7 cm. from the tip of the temporal lobe and if this ablation is rigorously pursued to the point where all mesial temporal cortex is removed, there is danger of vascular deficit in some of the major Sylvian vessels and/or the anterior choroidal artery, either as a result of vascular spasm or retrograde thrombosis.

In considering the results obtained on schizophrenic patients without epilepsy it should be stressed that in the majority of cases probably the only therapeutic attempt should be some form of frontal lobotomy, usually bilateral but occasionally unilateral. However, in some recalcitrant cases bilateral frontal and bilateral anterior and mesial temporal excisions may be necessitated. Of 17 patients with these latter procedures, 6 have been greatly improved, 6 were somewhat improved, and 5 were essentially unimproved. No significant difference in results was observed in patients with bilateral mesial frontal lobotomy (i.e., section of both mesial frontal quadrants) as compared with those who had bilateral frontal orbital lobotomy (i.e., section of both orbital quadrants). Our principal guide for temporal lobe surgery in psychotic patients was the almost invariable finding of spiking in the anterior temporal region with marked involvement of the uncus and the anterior and even the posterior portion of the hippocampus. But to avoid deficits, which will be discussed later, temporal resections for psychosis should probably be limited to the far anterior portion of the lateral temporal lobe, while the mesial resection may include the uncus and anterior hippocampus. The removal of the anterior portion of the temporal lobe may be 3 to 4 cm. posterior to the anterior temporal tip on the lateral surface of the lobe, while mesially the removal may be 5, 6 or 7 cm. from the anterior tip of the temporal lobe. This excision differs rather radically from that of Bailey *et al.*[4] on patients with psychomotor epilepsy but without psychosis, in that the lateral cortex removals are more limited in our patients, while the mesial temporal removals are more extensive.

Because of the reports of Klüver and Bucy[21] regarding the changes seen in monkeys with bilateral temporal lobectomy, we were very hesitant to carry out radical bilateral temporal excisions. However, 2 patients who were extremely psychotic and emotionally disturbed, assaultive and completely unmanageable had extensive bilateral temporal removals; 6–8 cm. of each temporal lobe were ablated, both mesially and laterally. This resulted in marked loss of emotional response to various stimuli, markedly increased (or at times decreased) food intake, very little response to human contact, lack of environmental contact except for an interest in eating periodically. Most of the time the patient sat or slept quietly; this lethargy was interrupted by the exhibition of some anxiety when the desire to urinate or defecate arose. The recent reports by Terzian and Dalle Ore[36] and by Petit-Dutaillis *et al.*[30] have emphasized similar changes in behavior in their cases

of extensive bilateral temporal ablations for psychomotor epilepsy without psychosis. As Penfield and Jasper,[28] MacLean[23] and Milner and Scoville[27] have emphasized, there is marked danger of loss of memory; this may occur with either lateral temporal or hippocampal resection. It is usually minimal after unilateral temporal ablations, but may be marked if a bilateral resection includes more than 5 cm. of the anterior temporal lobe from the anterior tip posteriorly. There is ample evidence that radical bilateral temporal lobectomy results in such serious defects that it should not be performed.

Postoperative seizures occurred in 3 patients who did not have seizures prior to surgery. These are well controlled on small dosages of Dilantin.

As previously stated, there were 5 deaths. The causes of death in 3 cases, in which autopsy was obtained, were as follows: pyoventriculus in 1 patient, recurrent postoperative bleeding with midbrain hemorrhage in another, and midbrain hemorrhage in a third. In none of these 3 patients were depth electrode needles inserted into the central gray masses or brain stem. In the other 2 cases, in which unfortunately an autopsy could not be obtained, there were postoperative coma and bronchopneumonia. These patients had had thalamic needles inserted at operation without any signs of bleeding as far as could be ascertained at the time.

SUMMARY AND CONCLUSIONS

The site of the primary discharge in 13 patients with psychomotor epilepsy and in 62 patients with psychosis and without clinical evidence of epilepsy has been determined electroencephalographically by means of multiple recordings from the scalp, surface of the brain, and depths of the brain, using 32 channels of simultaneous recording. Evidence from this study indicates that the spikes that usually appear with scalp recordings in the anterior temporal region of patients with psychomotor epilepsy almost invariably show in depth electroencephalography as spike seizure activity in the anterior and mesial portions of the temporal lobe.

The next most common areas from which seizure activity can be obtained in patients with psychomotor epilepsy and/or psychosis are the mesial orbital surface of the frontal lobe and the posterior mesial temporal lobe. The thalamus showed no evidence of primary involvement in this group of patients.

Further study is required to determine whether mesial temporal and mesial orbital frontal discharges occur in patients who have neither psychosis nor epilepsy.

In some cases of psychomotor epilepsy, anterior temporal lobectomy with the additional removal of a large portion of the mesial surface of the temporal lobe gives marked amelioration of symptoms. However, in cases of a frontal lobe involvement or with severe psychiatric manifestations, combined frontal lobotomy and unilateral or bilateral anterior temporal resections may be needed to produce a significant therapeutic effect. Radical bilateral temporal lobectomy should not be performed.

The operative series is still too small, the time after surgery too short and the number and variety of operations too great to draw any definite conclusions as to whether or not an improved surgical treatment of psychomotor epilepsy can be developed. We can only point to hopeful surmises which will be proved or disproved by future experience.

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POSSIBLE FACTORS IN THE DEVELOPMENT OF THE ARNOLD-CHIARI MALFORMATION

ALEXANDER BARRY, PH.D., BRADLEY M. PATTEN, PH.D., AND BRUCE H. STEWART, M.D.*

Department of Anatomy, University of Michigan Medical School, Ann Arbor, Michigan

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ARNOLD,[2] in 1894, reported on a series of hydrocephalic individuals exhibiting, also, congenital defects in the region of the hindbrain. Although these cases varied considerably, the essential condition was that of a herniation of tongue-like processes of cerebellar tissue into the cervical canal. In 1891 and 1896 Chiari[5,6] described a series of similar cases in which a distorted medulla, as well as cerebellar tissue, was within the cervical canal. In these cases the tongues of cerebellar tissue were so bound down to the medulla that usually there was interference with the passage of cerebrospinal fluid through the roof of the 4th ventricle. Schwalbe and Gredig[21] suggested that such cases formed a logical entity which they called the Arnold-Chiari malformation.

The frequent association of an Arnold-Chiari malformation with myeloschisis has led certain workers to postulate a causal interrelation between the two conditions (see, for example, Penfield and Coburn,[18] and Lichtenstein[12]). It is well known that, during the middle trimester of gestation, the spinal column increases in length more rapidly than the spinal cord.[11,16,22] Normally at this time the cephalic part of the cord is more securely anchored than its caudal region. This is not only because of its fixation by the brain within the developing cranium, but also because of the relatively more advanced state of development of the spinal nerves cephalically. As a result of the differential in rate of growth and the cephalic anchorage, the lumbosacral part of the cord slides cephalad within the neural canal with the concomitant elongation of the lumbosacral nerve roots to form the cauda equina. If during this period there is a lumbar or a sacral myeloschisis the spinal cord has an abnormal point of fixation caudally. This undoubtedly subjects it to abnormal traction, and the inference that such traction might pull the medulla and cerebellum caudad through the foramen magnum, is plausible and has all the allure of a "simple mechanical explanation" of the genesis of the Arnold-Chiari malformation. The validity of the traction interpretation has been called in question by a number of workers.[1,3,13–15]

MATERIAL

There are available in the University of Michigan Embryological Collection five human embryos showing various stages in the development of

* The participation of Dr. Stewart in this work was made possible through a summer research fellowship granted to him while he was a medical student.

myeloschisis. Three of these specimens have been reported previously.[17] The youngest of this series and one of the other available specimens were too young to have had time to develop an Arnold-Chiari malformation. The two older ones in Patten's series and another specimen of promising age were dissected to expose the entire length of the spinal cord and the brain. These embryos, constituting the basis of the present report, were: EH 220, 49 mm. C-R, estimated fertilization age, 10 weeks; EH 604, 141 mm. C-R,

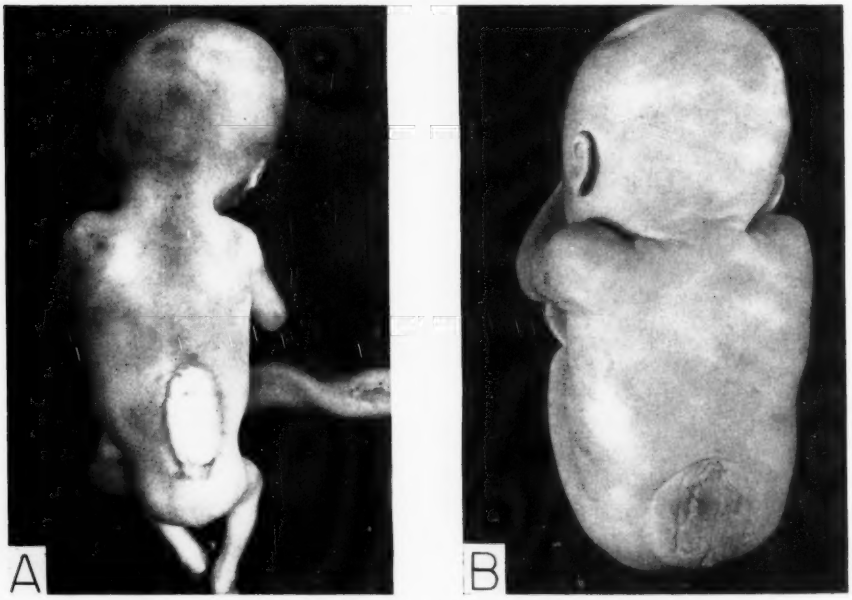

FIG. 1. Dorsal view of two fetuses showing myeloschisis in the lumbosacral region. (A) Fetus of 49 mm. (about 10 weeks). On dissection this fetus showed conditions indicative of a beginning Arnold-Chiari malformation. (B) Fetus of 160 mm. (about 18 weeks). This fetus showed a clear-cut Arnold-Chiari malformation of the hindbrain.

estimated fertilization age, 17 weeks; and EH 213, 160 mm. C-R, estimated fertilization age, 18 weeks. All measurements given were made after fixation. Fig. 1 shows the external appearance of the youngest and oldest of these abnormal fetuses. Fig. 2 compares the dissected appearance of the region of myeloschisis of the 18-week specimen with the same region of a control fetus. The two older specimens showed an unmistakable Arnold-Chiari malformation (Fig. 3), and the youngest showed conditions indicative of an incipient Arnold-Chiari.

This material, therefore, offered an unusual opportunity to evaluate the effects of the traction resulting from the myeloschisis. Determination of the territory in which there was a departure from the normal angulation of the spinal nerves will be seen to give an assessment of the location and extent

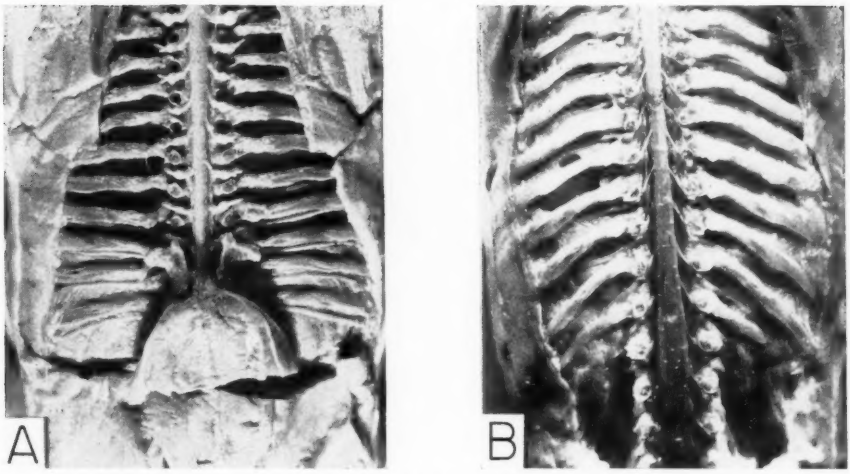

FIG. 2. (A) Dissection of lumbosacral region of the 18-week fetus illustrated in Fig. 1B, showing the myeloschisis and the relations of the spinal cord and nerves immediately cephalic to the defect. The cut across the myeloschisis indicates where a section was removed for histological study. (B) Dissection of a normal fetus of approximately the same stage of development for comparison with A.

of the abnormal traction. A concurrent study of the angulation of the spinal nerves at different cord levels, at various stages of normal development, afforded the necessary basis of comparison.[4]

GROWTH MECHANICS INVOLVED

PRIMARY TRACTION FROM MYELOSCHISIS

In the course of normal development the difference in rate of growth between the vertebral column and the spinal cord begins to become evident in

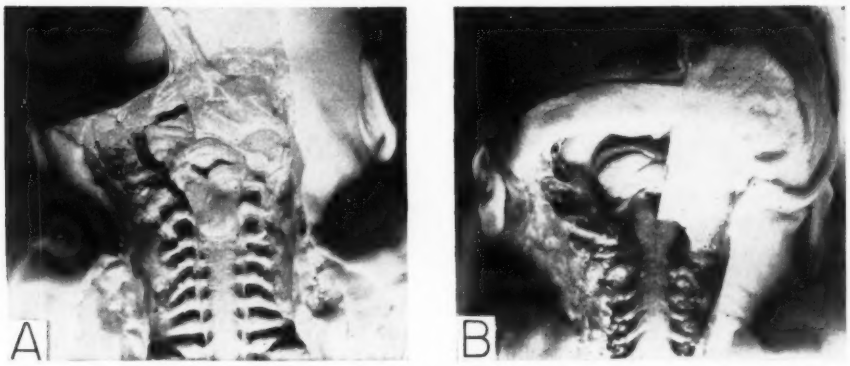

FIG. 3. (A) Dissection of the occipitocervical region of the fetus illustrated in Fig. 1B, showing the existence of a typical Arnold-Chiari malformation. (B) Dissection of a normal fetus of corresponding age for comparison.

embryos of about 35 mm. C-R (9 weeks). The tension thus developed is exerted as a stretching force upon the cord, attenuating its caudalmost segments into the filum terminale, and drawing out the lower spinal nerves into the cauda equina. In the case of a fetus with myeloschisis, this differential growth between the axial skeleton and central nervous system is present, but the defect of the spinal cord alters its morphological expression. The unclosed region of the cord is firmly attached to the surrounding structures and the nerves emerging from its middle part change their original right-angled course relatively little. This indicates that the cord in the region of

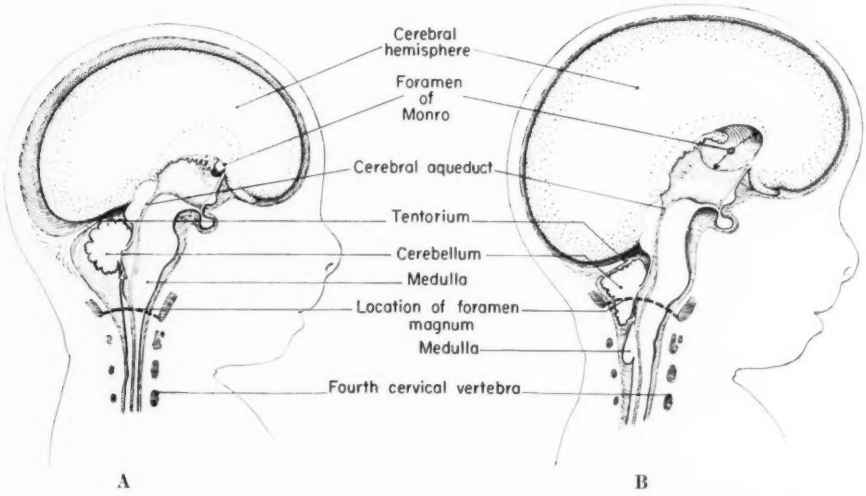

FIG. 4. Diagrams showing in sagittal plane the relations of brain and upper cervical spinal cord to the surrounding bony structures. (A) Normal fetus of approximately 18 weeks. (B) Fetus of 160 mm. (18 weeks) with the Arnold-Chiari malformation.

the myeloschisis remains essentially at its level of origin. If the defect is in the lower part of the spinal cord no cauda equina is formed. Russell[19] has, however, reported a case in which the anchorage caused by the myeloschisis was so high in the thoracic cord that there was still sufficient length of unaffected cord below the defect to permit the formation of a cauda equina. By reason of the location of anchorage in a lumbosacral myeloschisis, the stretching force applied to the spinal cord during development cannot be dissipated by an attenuation of its caudalmost segments. Instead the stretching must take place in that portion of the cord cephalic to the defect. In order to determine how far cephalically the abnormal tension had been exerted upon the spinal cord, measurements were made of the lengths of the various cord segments in the fetuses with myeloschisis and in normal fetuses of comparable age.

A spinal segment was defined as that length of the spinal cord that gives

rise to the dorsal rootlets of a single spinal nerve (Fig. 5). The distance between these markers was measured to the nearest tenth of a millimeter with a vernier caliper, under a dissecting microscope. In none of the specimens was it found feasible to measure the length of the 1st cervical segment because of the variable and frequently uncertain position of the most cephalic

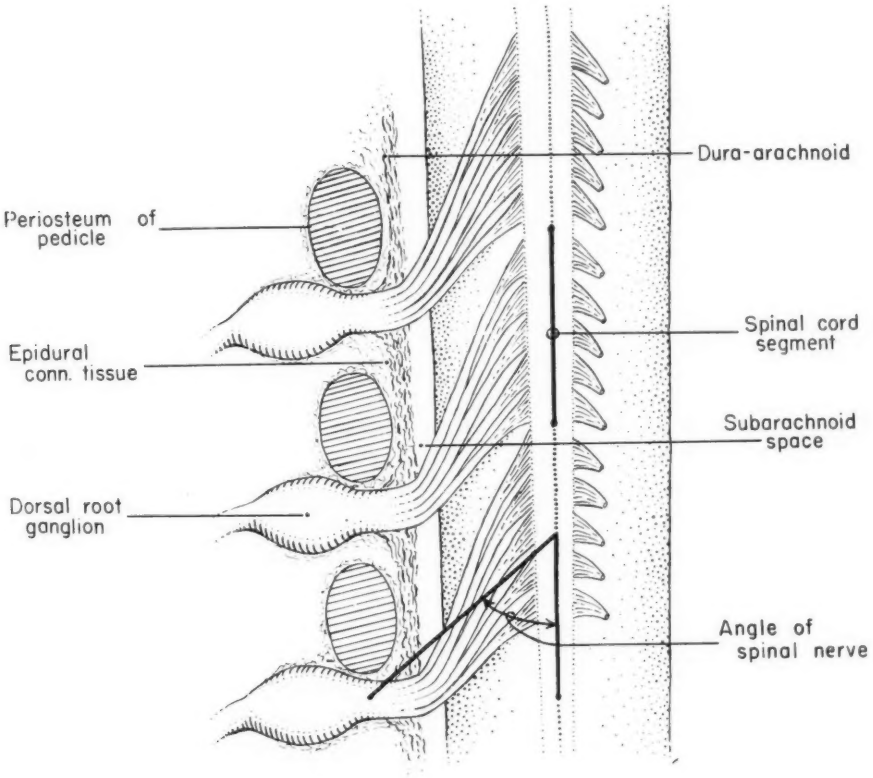

FIG. 5. Diagram showing method of measuring angulation of spinal nerves and length of spinal cord segment.

rootlet of the 1st cervical nerve. Fig. 6 presents graphically the lengths of the spinal cord segments of our two oldest fetuses with myeloschisis, as compared with those of a normal fetus of like age. It is clear that in both of the abnormal fetuses the spinal cord segments immediately cephalic to the defect are longer than normal. This excessive length becomes progressively less cephalically, and within four or five segments the spinal cord appears normal. This indicates that the tension exerted by the anchoring of the myeloschisis is dissipated within five segments.

The spinal cord of the youngest specimen (49 mm. C-R) did not show any measurable stretching effect. This is to be expected because at this age the differential growth of the spinal cord and vertebral column has scarcely begun, as evidenced by the fact that the end of the spinal cord is only a half segment from the end of the vertebral canal.

Suggestive as it is, the foregoing analysis of the extent of stretching of spinal cord segments does not absolutely preclude the possibility of some

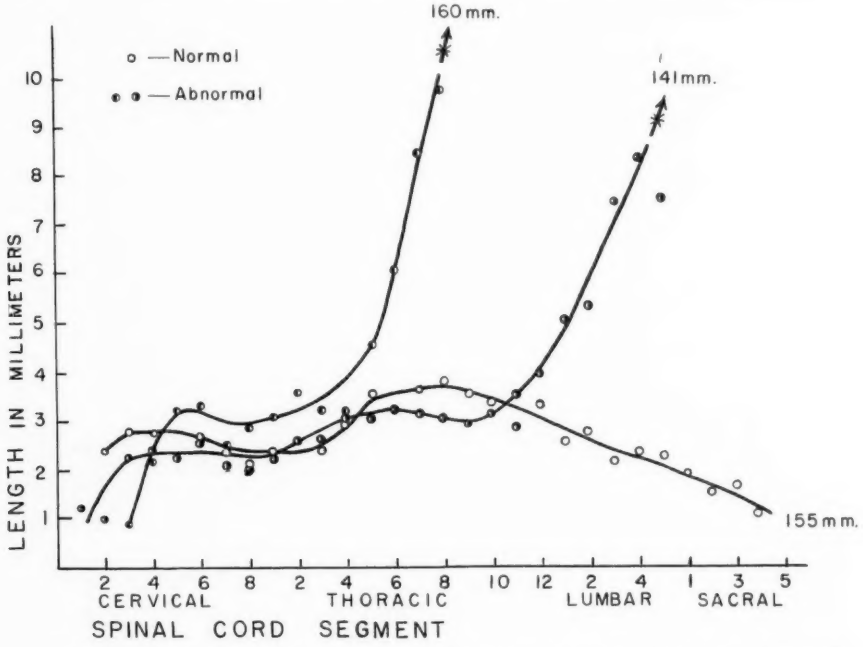

FIG. 6. Graph showing the length of the various spinal cord segments of two fetuses with myeloschisis as compared with a normal fetus of comparable age. In the plots for the abnormal fetuses the asterisk indicates the cephalic margin of the area involved in the myeloschisis.

tension being operative at higher levels. It is still theoretically possible that traction might be exerted on the hindbrain through the apparently normal cord or its meninges. This possibility can, however, be ruled out by an analysis of the angulation of the spinal nerves.

The course of the spinal nerves within the vertebral canal, especially in the older fetuses, is not straight. They tend to run in a curved path, which is accentuated by the attachments of the developing dural sheath (Fig. 5). For this reason it was important to establish criteria for measuring the angulation of the spinal nerves which would be comparable at all levels of the cord and at all ages. Since the immediate reason for making these measurements was to analyze the effects of the differential growth between

cord and vertebral column in cases of myeloschisis, the criteria for defining the angle of the spinal nerve were based on the relative positions of the spinal cord and the vertebrae. The angle of a spinal nerve, therefore, was taken as the angle between the mid-sagittal plane and a line passing from the midpoint of the spinal cord segment to the middle of the spinal nerve at the vertebral foramen (Fig. 5).

The results of such measurements can be best presented graphically. The data for a 141 mm. fetus with myeloschisis have been assembled in Fig. 7A and similar data for a 160 mm. fetus in Fig. 7B. On the right of the axial line in each case is indicated the normal angulation of the spinal nerves as determined by Barry.[4] On the left of the axial line is indicated the course followed by the spinal nerves in a specific case of myeloschisis. A study of the graph of Fig. 7A will show that the angulation of the spinal nerves at thoracic levels is essentially normal. It is equally apparent that the four spinal nerves immediately cephalic to the myeloschisis are not normally angulated. Instead of coursing caudally toward its foramen of exit, the 5th lumbar nerve slopes cephalad. The next three nerves in the series, because of the stretching of their respective cord segments, lie progressively nearer to their normal positions with respect to the vertebrae, and their angulation progressively approaches the normal.

Since the 1st lumbar nerve has an essentially normal angulation, this can only mean that the 1st lumbar cord segment is in a normal relationship to the vertebrae. On this basis, therefore, as well as on the basis of the length of the cord segment, one must conclude that the traction exerted upon this segment is normal, and that the abnormal tension caused by the myeloschisis has been dissipated within four segments of the cord.

Fig. 7B compares the angulation of the spinal nerves of the 160 mm. C-R fetus having myeloschisis with the nerve angulation of a normal fetus of comparable age. In spite of the fact that in this case the cord defect extends up to low thoracic levels, one is led to the conclusion that here, also, the abnormal traction has been dissipated within four cord segments.

Fig. 8 shows, in more detail, the course of the 4th and 5th lumbar nerves of the 160 mm. fetus as well as those emerging from the region of myeloschisis. The manner in which the nerves tend to radiate out from the massive spinal defect is in harmony with the findings of other investigators (e.g., Russell[19]). This pattern indicates that, during the period after the vertebral column had been established, the cord, although overmassive in the region of the myeloschisis, had failed to elongate as rapidly as the vertebrae underlying it. As a result the roots of the nerves originating from its cephalic part were drawn caudad with respect to their vertebral foramina, while the roots of the caudalmost nerves were drawn cephalad. Only the nerves emerging from the middle portion of the defect retain the right-angled course one would expect from their anchorage. This relative shortening of the myeloschisis means that the caudal edge of the segment of the spinal cord immediately cephalic to the defect must have been pulled caudad from its original

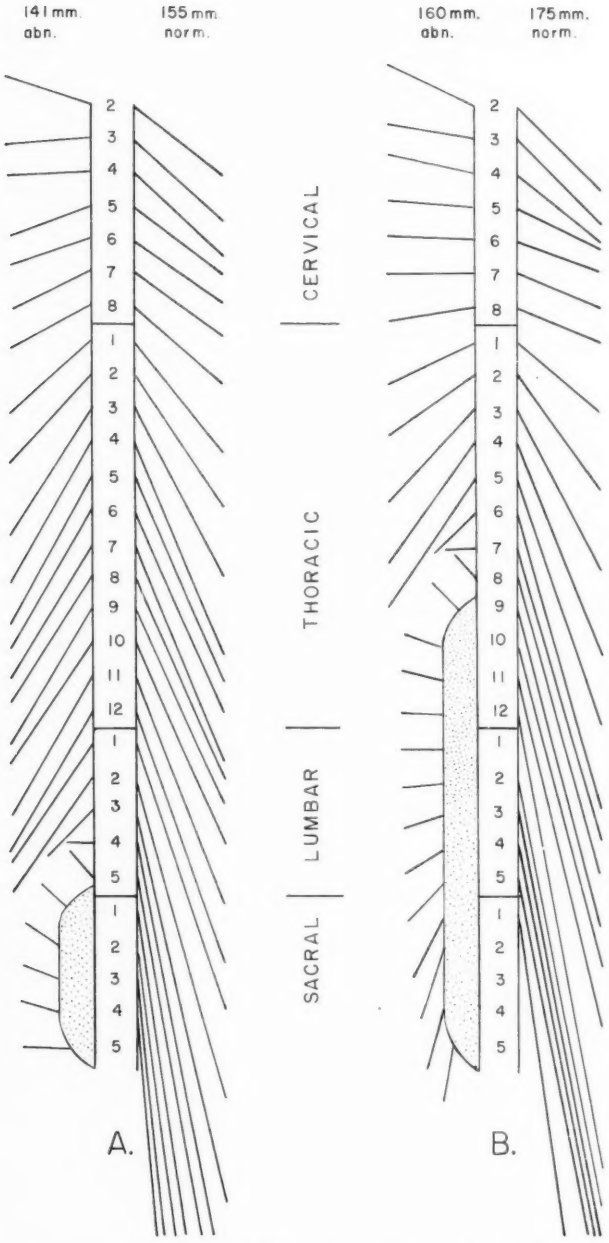

FIG. 7. Two diagrams showing, on the right in each case, the normal angulation of the spinal nerves, and on the left the distortion of the normal pattern in a specific case of myeloschisis. (A) Fetus of 141 mm. (about 17 weeks). (B) Fetus of 160 mm. (about 18 weeks).

position. The tension exerted upon this segment from above has not caused it to stretch enough to keep its midpoint at its level of origin. As a result its nerve angulation is actually the reverse of normal (Fig. 8). An essentially similar condition was exhibited by the 141 mm. fetus.

It should be noted also that the dural sheath of the spinal cord is firmly

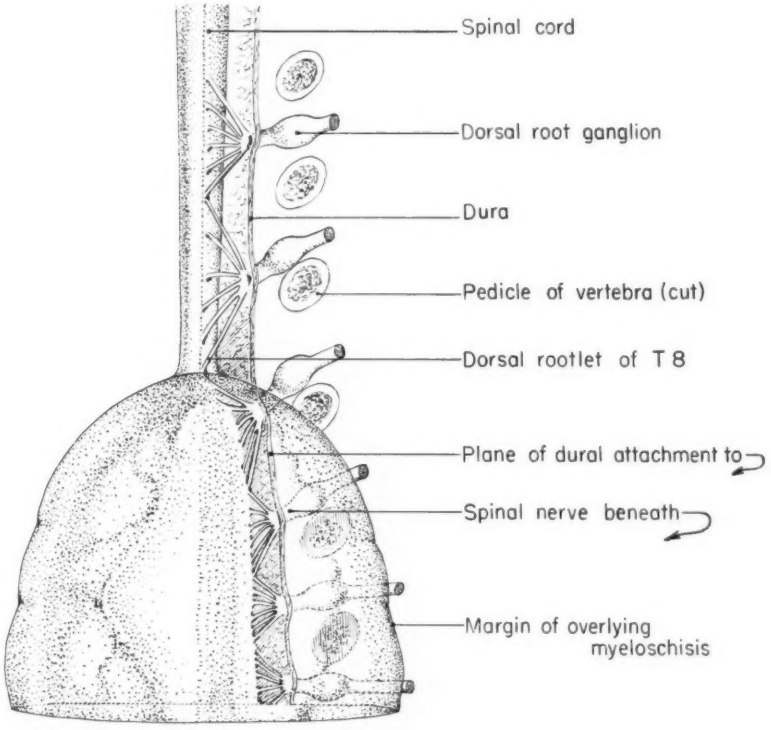

FIG. 8. Schematic drawing, from the fetus of 160 mm., of the cephalic half of the myeloschisis and the immediately adjacent cord segments, showing the relationship of the spinal nerves to the spinal cord, dura mater, and pedicles of the vertebrae. On the right the massively overgrown myeloschisis is represented as transparent so as to show the underlying structures. (Compare with Fig. 1B.)

attached to the cephalic edge of the myeloschisis. During development this tough sheet of connective tissue has not kept pace with the elongation of the vertebral column. Accordingly it is relatively short and draws the spinal nerves, especially those in the lumbar region, into an angled course within the vertebral canal (Fig. 8). Since the distance between the dura mater and the spinal cord is not great, that part of the nerve lying within the subarachnoid space is often difficult to follow (Fig. 3), and the true angle of the spinal nerve, as defined in this paper, may not be evident on casual inspection.

If the foregoing interpretation of the observed data is accepted, then one must conclude that the traction exerted by a myeloschisis located caudal to mid-thoracic levels cannot be effective in drawing the medulla and cerebellum caudally through the foramen magnum. One must, therefore, look elsewhere for an explanation of the herniation of the hindbrain into the cervical canal. In spite of being able to rule out traction from below as operative at cervical levels, it will be noticed that the upper cervical nerves are unmistakably abnormal in their angulation. This is obviously a result of the fact that the spinal cord segments giving rise to them lie abnormally far caudally. The probable reason for this can be more profitably discussed later, following an analysis of the region of the hindbrain.

RESULTS OF OVERGROWTH

Patten[17] has previously presented evidence that early overgrowth of neural plate tissue is an underlying factor in the genesis of myeloschisis. In view of this it seemed of interest to determine the size of other apparently unaffected regions of the nervous system. Because of the rarity and significance of these specimens, it seemed unwise to handle them in any manner that would destroy basic relationships. Therefore, the brain and cord were not removed for quantitative determination of the volume of the various parts. Instead their relative volumes were assessed in the following way. The dorsoventral and lateral dimensions of each of the spinal cord segments were measured at its midpoint. If one assumes that the cross section of the spinal cord is essentially elliptical, then the product of these two dimensions is directly proportional to the cross-sectional area of the cord segment at its midpoint. This value was multiplied by the length of the cord segment, to give an index that is directly proportional to its volume. These values are presented graphically in Fig. 9 for the two oldest fetuses with myeloschisis, as compared with similar data from a normal fetus of comparable age. It is clear that the volumes of the spinal cord segments cephalic to the myeloschisis are strikingly larger than normal, in spite of the fact that they have been stretched and are much thinner than the corresponding segments of the control fetus. This observation suggests a plausible extension of the line of reasoning previously outlined as to the causation of the myeloschisis. Take the 141 mm. fetus as a specific example. If Patten's interpretation is correct, there was sufficient overgrowth of neural plate tissue caudal to the 1st sacral segment to prevent its fusion to complete the neural tube. Study of the data obtained from assessments of the volume of the cord segments (Fig. 9) indicates that the overgrowth was not limited to the region in which it was sufficiently severe to cause myeloschisis. Some overgrowth extended cephalically as far as the 12th thoracic segment, but it was progressively less marked in the more cephalic segments. Thus segments from L4 to T12 of the neural folds, although they were not overgrown enough to prevent fusion, did give rise to an abnormally large spinal cord.

Fig. 10 compares the relative volumes of the spinal cord segments of the youngest specimen exhibiting myeloschisis (49 mm. C-R) with those of a

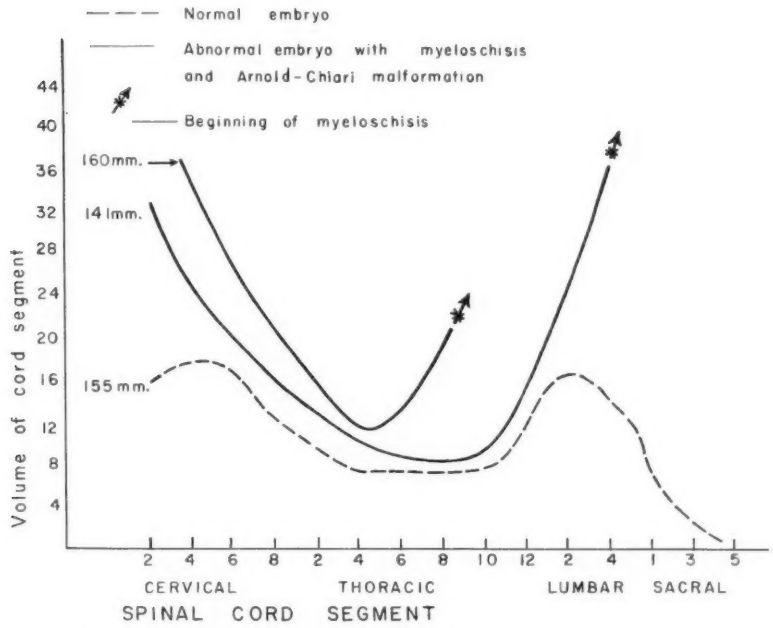

FIG. 9. Graph showing volume of the various spinal cord segments of the same two abnormal fetuses dealt with in Fig. 6 as compared with the same normal fetus.

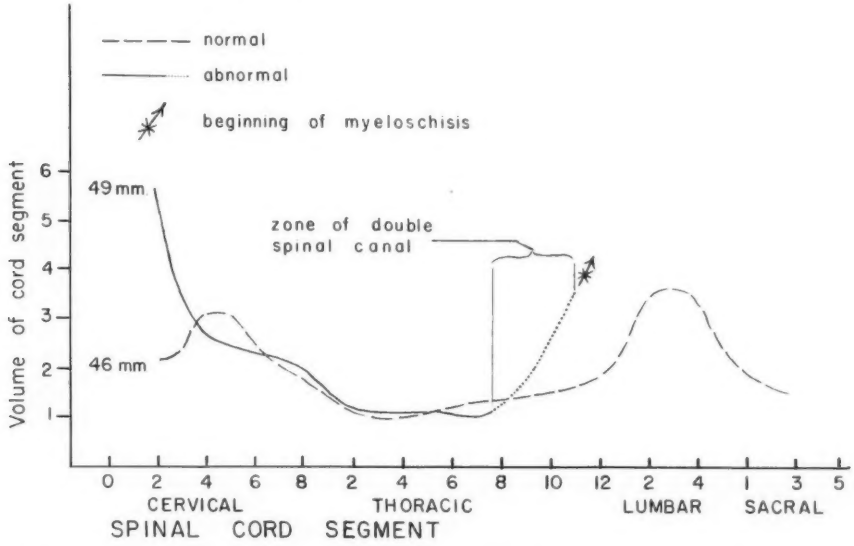

FIG. 10. Graph showing the volume of the various spinal cord segments of a younger fetus with myeloschisis (C-R 49 mm., about 10 weeks) as compared with a normal fetus of comparable age.

normal control fetus. In the abnormal specimen the myeloschisis extended cephalically to the 11th thoracic segment. In this case, as in the older fetuses, the cord segments immediately cephalic to the defect are overgrown, while those in the upper thoracic and lower cervical levels are within the normal range. This finding is of particular interest since this fetus is of such an age that the differential growth between the spinal cord and the vertebral column has not yet begun. This fact rules out the possibility that the overgrowth of the spinal cord might in some way be caused by the abnormal tensions exerted upon it as a result of the myeloschisis.

It should, perhaps, be stated here that "overgrowth" as used in this paper is a purely descriptive morphological term. It means simply that the tissue mass in question is too large as compared with the mass of that tissue in the normal fetus. The histological fixation of the available specimens was not sufficiently good to permit accurate differentiation of the cell types in the central nervous system. For this reason, although it appeared reasonably certain that the overgrown tissues contained an excessive number of cells, it was not possible to determine whether the overgrowth involved the neuroblasts, the spongioblasts, or both.

It is known from the work of Fowler[7] that when the neural folds of chick embryos are mechanically prevented from fusing in a region, the tissue of the spinal cord at the level of the resultant myeloschisis shows marked evidence of overgrowth. This phenomenon raises a question as to whether the overgrowth seen in the specimens reported here may not be secondary to a primary failure of the neural folds to fuse. Whatever the situation may be as to myeloschisis, this possibility may be ruled out for the region of the brain since here, and also in much of the spinal cord, there is demonstrable overgrowth in spite of the fact that fusion of the neural folds did take place.

The work of Giroud[8] has shown that when one experimentally causes an inhibition of the axial mesodermal structures over a limited area of the body such that the vertebral lengths are abnormally short, the neural folds, which increase in volume at a normal rate, are compressed cephalocaudally. As a consequence they appear too large in cross-sectional area. This cannot be the underlying cause of the defects seen in these specimens of the Arnold-Chiari malformation, since the vertebral lengths are normal as compared with the control specimens at those levels where the volumes of the spinal cord segments are markedly too large.

When it became apparent that the spinal cord was abnormally large at regions other than where it exhibited myeloschisis, it seemed pertinent to examine the brain as to normality of size. Although, for reasons previously mentioned, no volumetric determinations were made, configuration and linear measurements of the medulla and cerebellum of the 160 mm. C-R fetus indicate that its hindbrain is strikingly more massive than is that of a normal fetus of comparable age (Figs. 3 and 4). The medulla and the caudal part of the overgrown cerebellum lie outside the cranium and extend caudally to the level of the 4th cervical vertebra. The uppermost segments of the

spinal cord are compressed (Fig. 6) and the spinal nerves arising from them course cephalad to their foramina of exit, in the reverse of the normal direction (Fig. 7). The medulla shows a marked dorsal knuckling in the mid-line. Thus this fetus unquestionably has an Arnold-Chiari malformation, since it meets the essential morphological criteria established for this condition by Schwalbe and Gredig.[21] The fetus of 141 mm. C-R presents essentially the same picture, and for this reason it did not seem necessary to illustrate it.

In the fetus of 49 mm., the medulla and cerebellum were unmistakably overgrown in comparison with the control. The posterior fossa was abnormally small. The medulla lay within the cervical canal, and the caudal edge of the cerebellum protruded slightly through the foramen magnum. Thus the roof of the 4th ventricle was situated entirely within the cervical canal. It appears certain that this fetus would have acquired the conditions characteristic of an Arnold-Chiari malformation if it had lived a few weeks longer.

Fig. 4 compares the lateral appearance of the brain of the abnormal 160 mm. fetus with that of a control. It indicates clearly that the cerebral hemisphere of the abnormal fetus is overlarge. The tentorium cerebelli is displaced caudally, accounting for the small posterior fossa. It seems logical to assume that this displacement is the result of the overgrowth of the cerebral tissue. The fetuses of 141 mm. and also 49 mm. showed a similar picture of cerebral overgrowth.

Ingraham and Scott[10] described a condition of microgyria which they found consistently in a series of 20 cases of Arnold-Chiari malformation. This condition of a multiplicity of small gyri of the cerebral cortex might well be the final result of the overgrowth of the cerebrum that was found in all three fetuses in our series. It is pertinent that in one postnatal case of the Arnold-Chiari malformation that came to necropsy at the University of Michigan Hospital,* a finding was made of microgyria of the cerebral cortex, and in spite of the presence of hydrocephalus the cerebrum was found to be of abnormally great weight.

SECONDARY HYDROCEPHALUS

On dissection of the oldest fetus with Arnold-Chiari malformation in our series (160 mm. C-R), there was clear evidence of hydrocephalus. The lateral ventricles were enlarged although the cortex was not yet conspicuously thinned. The interventricular foramina were dilated to an oval measuring $9 \times 7\frac{1}{4}$ mm. (Fig. 4). In the two younger specimens there was no discernible evidence of hydrocephalus. The midbrains of all three abnormal fetuses were removed and sectioned serially. A study of these series showed that the cerebral aqueduct was patent throughout its entire length in all cases. It is clear that the hydrocephalus evident in the oldest specimen could not have

* This specimen was made available through the courtesy of Dr. Edgar A. Kahn, Section of Neurosurgery, Department of Surgery; and Dr. Konstantin Scharenberg, Director of the Neuropathological Laboratories of the Neuropsychiatric Institute, University of Michigan Medical School.

been caused by abnormal blockage of the flow of cerebrospinal fluid at the level of the midbrain. In view of the mass of hindbrain material that is herniated through the foramen magnum, it can be explained plausibly on the basis of a blockage of the subarachnoid space at the level of the foramen magnum. This is in accord with a theory proposed by Russell and Donald.[20]

SECONDARY EFFECTS OF FIBROUS ANCHORAGE ON THE HINDBRAIN

It is of significance that the embryonic specimens of the Arnold-Chiari malformation reported here differ in certain details from the typical pattern commonly seen after birth. In the fetus the entire medulla and the caudal portion of the cerebellum have been forced into the cervical canal. Postnatally the usual findings are tongue-like processes of cerebellar tissue within the cervical canal, bound to the dorsal surface of the medulla by thickened meninges. The major portion of the cerebellum, which lies in the posterior fossa, is typically hypotrophic and poorly differentiated as to vermis and hemispheres. This difference between the morphology of the region of the hindbrain as we found it in the fetal material and that of the postnatal individual may be explained on the basis of changes in differential growth occurring during the second half of gestation.

In the fetuses of 141 mm. and 160 mm., the connective tissue of the dural sheath is beginning to bind the caudal portion of the cerebellum which lies in the cervical canal to the medulla and to the neural arches of the cervical vertebrae. This is a logical consequence of the fact that the medulla and the cerebellum are abnormally compressed within the confines of the upper cervical canal. The firmest part of this attachment might be expected to develop at either side of the mid-line where the relatively massive tissue of the rhomboid lip comes into closest contact with the developing cerebellar hemispheres. An assumption that, in later stages of development, growth is such that the cerebellum fails to maintain its early excessive size, possibly as a result of disturbed vascular supply, would account for the hypotrophic condition of the cerebellum frequently reported in cases of the Arnold-Chiari malformation. Moreover, if the skull developed in such a manner that the posterior fossa continued to enlarge relatively normally, then there would be a tendency for the hindbrain to be retracted cephalad through the foramen magnum. If this occurred, the two portions of the cerebellum that were anchored by dural adhesions within the cervical canal would be attenuated to form the tongue-like processes seen so typically in postnatal cases. These processes would then be under such tension that they would tend to retract toward the brain if their dural attachments were cut. Such a retraction has been reported by Penfield and Coburn[18] and by Lichtenstein[12] as occurring during operative procedures.

If the medulla is so firmly anchored within the cervical canal that it can not be retracted, as might well be the case if it is markedly overgrown, then it would present the typical postnatal picture of the Arnold-Chiari malformation. If, however, its anchoring is less firm, as it would probably be when

it is less enlarged, then the medulla might be retracted into a nearly normal position within the cranial cavity. This would result in one of the types of malformation reported by Arnold[2] and Chiari,[6] in which the defect consisted only of cerebellar processes projecting into the cervical canal. Variations in the degree of overgrowth and in the firmness of fibrous anchoring could account for this and other variations in the morphological findings reported in cases classified within the general category of Arnold-Chiari malformations. The "knuckled" appearance of the medulla seen in differing degrees can be regarded plausibly as the result of the variable amount of overgrowth in length and circumference of the embryonic medulla while its dural attachments retain it within a relatively short length of the cervical canal.

Thus, although the traction resulting from abnormal anchoring of the spinal cord by a lumbosacral myeloschisis cannot be regarded as being the primary cause of herniation of the hindbrain, localized meningeal traction during the second half of gestation may well play an important secondary role in the modeling of the definitive morphological pattern seen in cases of the Arnold-Chiari malformation.

SUMMARY AND CONCLUSIONS

From these observations one may arrive at the following tentative interpretation. The primary departure from normality in the genesis of an Arnold-Chiari malformation is overgrowth of the central nervous system, commencing before the fourth week of development. The overgrowth continues during the regional differentiation of the brain and cord and involves different areas to different degrees.

As a working hypothesis one may outline a logically correlated sequence of events. In the cases presented here the most striking overgrowth was in the lumbosacral region of the spinal cord. The medullary folds of this region early attained such a size as to prevent the normal closure of the neural tube, thus giving rise to the myeloschisis. Other levels of the developing central nervous system were involved to a lesser degree, and closure of the neural folds took place. In the specimens analyzed in this report the lower cervical and the thoracic segments of the spinal cord were involved minimally in overgrowth. The volume of the midbrain and the diencephalon could not be estimated, and so one cannot be sure whether or not they were affected. In certain other areas, however, there was enough overgrowth to result in a neural tube of excessive size.

It is perhaps significant that in one of our specimens (EH 220) there was a doubling of the neural canal immediately cephalic to the myeloschisis. A double neural canal has been reported to be associated with a double notochord in some abnormalities.[9] In our specimen, however, there was but a single notochord. It seems probable, therefore, that the doubling of the neural canal was the result of the excessive growth of the neural folds sufficient to distort but not prevent their fusion, rather than being caused by any possible induction effects from an abnormal notochord.

At the level of the myeloschisis, the margins of the enlarged neural tube are firmly anchored to surrounding structures. Moreover, at all levels of the spinal cord except where there is a myeloschisis there is an essentially normal vertebral canal. This means that the neural canal is much too small to accommodate the overgrown area. Therefore a cord with myeloschisis is restrained by the vertebral arches cephalic to it as well as being anchored by dural adhesions.

In the unaffected regions the differential growth of the vertebral column of the spinal cord exerts a traction on the cord in a manner which, under normal circumstances, produces the cauda equina. In embryos with myeloschisis this traction stretches the segments of the spinal cord immediately cephalic to the defect and, in spite of the fact that the cord in this region was originally more massive than normal, makes it appear strikingly slender. This traction, however, is dissipated within four segments, as is evidenced by the angulation of the spinal nerves. Traction, therefore, cannot be invoked as a causal factor in the caudad displacement of the rhombencephalon characteristic of the Arnold-Chiari malformation. This being the case, one must look for some other explanation of the rhombencephalic herniation.

Since it is evident that in these cases overgrowth of the central nervous system is one of the underlying factors, it is logical to examine the possible effects of the increased volumes of the intracranial parts of the central nervous system. Pursuing this line of reasoning, the excessive volume of the cerebrum shown to exist in our cases may be regarded as responsible for the fact that the tentorium cerebelli lies more caudally than is normal (Fig. 4). As a result the posterior fossa is abnormally small. Thus there is involved not only overgrowth of the cerebellum and medulla themselves, but also the fact that they are forced to develop in a space that becomes progressively less and less adequate. As an inevitable result they gradually protrude through the foramen magnum down into the cervical canal. This herniation eventually blocks the subarachnoid space at the foramen and as a result a progressive hydrocephalus is initiated. In the oldest fetus in our series (18 weeks) this condition was just beginning to be evident (Fig. 4B).

The protrusion of the hindbrain into the cervical canal necessarily displaces the uppermost segments of the cervical cord tailwards. As a result these segments are compressed cephalocaudally and their nerve roots show an angulation that is the reverse of the normal. This is, however, not the result of traction from below, but of growth pressure from above. It is to be expected that there will be variability between individual cases with respect to the locations and degrees of overgrowth as it affects the central nervous system. Thus, in rare cases, only the brain may be involved in overgrowth, resulting in an Arnold-Chiari malformation of the hindbrain without an accompanying myeloschisis. Conversely, one might find a case in which overgrowth was limited to the spinal cord, producing a myeloschisis in an otherwise normal individual.

Thus we believe that all the conditions commonly seen in cases of

myeloschisis and Arnold-Chiari malformations may be explained logically on the basis of different degrees of overgrowth involving several parts of the neural tube. There is no need to postulate traction on the rhombencephalon exerted through a structure with as little tensile strength as the embryonic spinal cord. Moreover, the hydrocephalus that frequently—but not always—accompanies such conditions can be more logically regarded as a sequel to, rather than a cause of, the protrusion of the medulla and the cerebellum into the cervical canal.

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HISTOPATHOLOGICAL CHANGES PRODUCED BY IMPLANTED ELECTRODES IN CAT BRAINS

COMPARISON WITH HISTOPATHOLOGICAL CHANGES IN HUMAN AND EXPERIMENTAL PUNCTURE WOUNDS*

JAMES C. COLLIAS, M.D.†, AND ELIAS E. MANUELIDIS, M.D.
Department of Pathology, Yale University School of Medicine, New Haven, Connecticut

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With the introduction of the Horsley-Clarke[13] stereotaxic instrument in 1908, a method became available for the investigation of the physiology of the central nervous system which has the advantage of precise localization to specific structures. Implantation of electrodes provided neurophysiologists with a useful method in studying neuronal mechanisms. With the development of the chronic electrode technique by Loucks[16] and its wide application in animals by Hess,[12] it became possible to study the relation of functions to structures of the nervous system in animals avoiding anesthesia, chemical restraint and extensive trauma. This technique has been further extended recently to humans suffering from neurological and psychiatric diseases.[2,3,6,10,11,18,27–30]

One of the questions that has arisen out of the technique of implanting electrodes, and which has stimulated the present work, is the extent and the amount of tissue destruction and reaction caused by the insertion of electrodes into brain tissue and the effect of the prolonged presence of such a foreign body. This problem has assumed paramount importance since features of this destruction must be kept to a minimum if analyses of the physiologic results are to be meaningful, particularly in reference to possible residual damage in humans.

Although of prime importance to investigators, a review of the literature has failed to reveal a detailed chronological study of the finer microscopic changes in the central nervous system that take place consequent to implanted electrodes. The neurophysiological literature contains a paucity of detailed histopathological examinations of sacrificed experimental animals. Many investigators have described the pathology in such general and nondescript statements as a "slight," "moderate," or "mild" gliosis for varying distances around the electrode track, while others have given no account of the histopathological characteristics of the electrode tracks and surrounding tissue. Fisher and Sayre[9] found evidence in studies on animals that the reaction around the electrode may occur within 1 mm. from the track. Dodge *et al.*[8] have recently reported minimal microscopic changes in 1 human 19 months after intracerebral electrography.

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† Now with the Department of Surgery, Yale University School of Medicine.

In view of the lack of chronological studies concerning the extent of mechanical destruction and reaction caused by implanted electrodes in the brain, it was felt that it would be both interesting and rewarding to investigate this problem in animals sacrificed after varying time intervals. It is planned to compare the data obtained in this experiment with studies reported in the literature dealing with puncture wounds of the brain in both humans and experimental animals.[1,15,19,20,25,31,32]

MATERIAL AND METHODS

Construction of Electrodes. The electrodes employed were of the multilead type described by Delgado.[5] Enameled stainless steel wire 0.005 inch in diameter was used. Tension was applied to 3 feet of wire to detemper it and pieces 3 inches in length were cut. The enamel was removed from the tips for 1 mm. Six wires were bound together with liquid Plexiglas with the tips approximately 2 mm. apart. Care was taken to get the surface as smooth as possible. The tip of the lead electrode was balled. The outside diameter of the electrode along that portion that entered the brain measured no more than 0.6 mm. The electrodes were washed with soap and water and sterilized in 1:1000 Zephiran solution for 1 hour prior to insertion. They were then washed thoroughly with sterile physiological saline immediately prior to insertion.

Operative Procedure and Implantation of Electrodes. Healthy adult cats (1.8 to 3.6 kg.) were used as experimental animals. The Horsley-Clarke[13] stereotaxic instrument was used for the placement of the electrodes. Aseptic technique was used throughout the procedure. Nembutal anesthesia was employed.

The hippocampal, caudate, mammillary, and septal regions were chosen as sites for implantation. Two electrodes were placed in each animal, one in each cerebral hemisphere. Those animals that had a hippocampal electrode on one side had a mammillary electrode implanted on the other. Septal and caudate electrodes likewise were implanted in the opposite hemisphere of the same animal.

Postoperative Course. Postoperatively the experimental animals were kept in cages with the electrodes in place until the time of sacrifice. All the animals, except for the 2 that died, remained in apparently healthy condition. The skin over the head usually remained dry and growth of hair was normal in the chronic animals. No antibiotic or sulfonamide powder was applied locally and no systemic antibiotic was given postoperatively. Local suppuration occurred minimally.

Sacrifice of Animals (Table 1). The acute animals were sacrificed at intervals of 24 hours, 3 days, and 7 days postoperatively. Chronic animals were sacrificed at intervals of 15 days, 1 month, 2 months, 4 months, and 6 months postoperatively. Two animals were included in each stage. It was hoped to include 1 cat with hippocampal and mammillary electrodes and 1 with septal and caudate electrodes in each stage. However, this was not possible because of the premature deaths of some animals. Only 1 animal is included in the 3-day and 4-month stages, because of the premature deaths of the other animals. All animals were sacrificed by first anesthetizing them and then perfusing them through the heart with bromformal solution. The electrodes were carefully lifted out of place. The skull was opened and the brain was removed and placed in bromformalin immediately.

Histological Techniques. After suitable fixation, frozen sections were cut at 20 micra through the longitudinal axis of the electrode track, using the method described by Marshall.[17] Sections from each brain were stained by the following meth-

TABLE 1

Animal No.	Time Intervals between Implantation of Electrodes and Sacrifice	Sites of Implantation of Electrodes
1	24 hours	Hippocampal mammillary
2	24 hours	Hippocampal mammillary
3	3 days	Hippocampal mammillary
4	3 days*	Septal caudate
5	7 days	Septal caudate
6	7 days	Septal caudate
7	15 days	Hippocampal mammillary
8	15 days	Hippocampal mammillary
9	1 month	Septal caudate
10	1 month	Hippocampal mammillary
11	2 months	Hippocampal mammillary
12	2 months	Septal caudate
13	4 months	Septal caudate
14	4 months*	Hippocampal mammillary
15	6 months	Septal caudate
16	6 months	Septal caudate

* Animal died prematurely and was discarded from this study.

ods: (a) myelin stain of Schroeder, (b) glia fiber stain of Holzer, (c) Sudan IV for fat, (d) hematoxylin and eosin, (e) panoptic stain of Hortega, (f) triple silver carbonate impregnation, and (g) astroglia stain with silver carbonate. The last three mentioned techniques were used according to modifications recommended by Scharenberg.[26]

PATHOLOGICAL CHANGES AT VARYING TIME INTERVALS AFTER ELECTRODE IMPLANTATION

A. MACROSCOPIC CHANGES

In general, gross inspection of the hemispheres of the brains revealed minimal changes. Localized abscesses or signs of meningeal inflammation were not found. Adhesions of the meninges at the point of entry of the electrode were found and in most cases could be easily broken by blunt dissection. Cat 1, however, revealed an extensive subdural hemorrhage involving most of one cerebral hemisphere.

B. MICROSCOPIC CHANGES

24-Hour Stage (*Cats 1 and 2*). The track was markedly irregular in contour and diameter. Extensive hemorrhage and necrotic debris partially filling the lumen of the track was the most prominent feature. The bleeding was more marked in the superior two-thirds of the track and tended to be decreased in the inferior portion. Around the track there was an irregular zone in which hemorrhages extended into the surrounding parenchyma in cylindrical forms of finger-like extensions (Fig. 1). These extended for 1 mm. at the most. Other more blunt hemorrhages extended for distances of 0.5–0.25 mm. into the surrounding tissue. The hemorrhage was found to infiltrate the meninges on the convexity of the brain for about 0.5 mm. bilaterally, and in 1 animal the lateral ventricle was filled with blood. In the inferior portions of the track, almost a complete lack of hemorrhagic infiltration was noted in the surrounding brain tissue.

Surrounding the hemorrhagic infiltration of the brain tissue, especially in the white matter, there was an area, measuring approximately 0.5–1 mm. in width, of more palely stained tissue, revealing sponginess and scattered petechial hemorrhages. Foci of the zone revealed, especially in the vicinity of the hemorrhage, complete necrosis. Petechiae were found in what appeared to be normal brain tissue approximately 1–1.5 mm. from the margin of the track. Fibrin was found within these petechiae although the red cells frequently outstripped the fibrin.

Large numbers of polymorphonuclear leucocytes were seen in the areas of hemor-

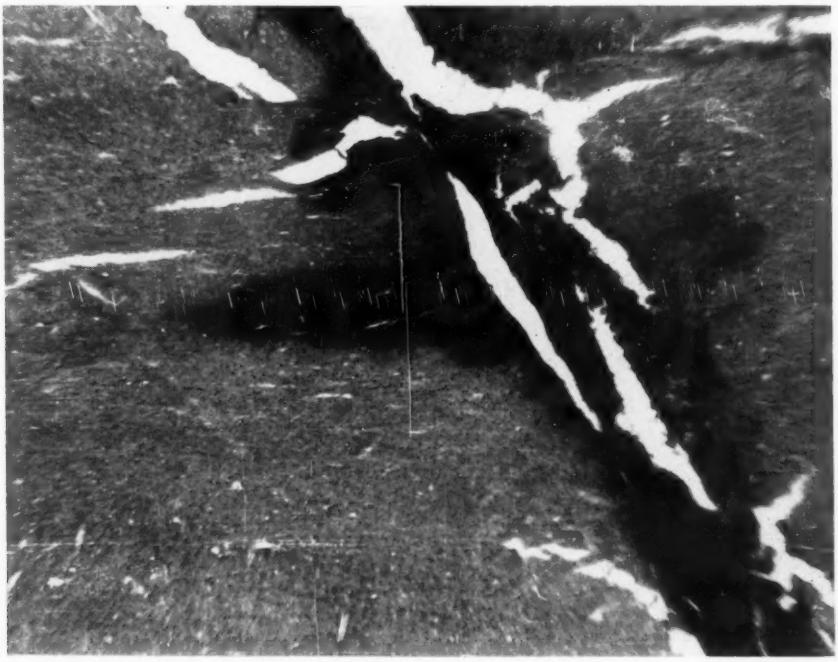

FIG. 1. *24-hour stage.* Central hemorrhage in the electrode track with finger-like extensions into the surrounding brain tissue, running parallel to the preserved myelinated structures. Hematoxylin and eosin, ×35.

rhagic infiltrations surrounding the track. In the inferior portion of the track, where the bleeding was almost exclusively restricted to the canal, only occasional polymorphonuclear leucocytes were observed. An intensive infiltration with polymorphonuclear leucocytes was present in those areas in which petechiae occurred. Phagocytic activity of leucocytes was evident.

Scattered irregularly in the immediate vicinity of the margins of the track were elongated, swollen, twisted and hypertrophic microglial cells (Fig. 2). In some regions these were present at distances of 0.5–1 mm. from the margin of the track.

Pyknotic oligodendroglia with irregular nuclear outlines were seen in the immediate margin of the track and in the neighborhood of petechiae. These altered cells were more numerous in the white matter.

Within the area of hemorrhagic infiltration, disintegrating astrocytes were observed. Nuclei with no recognizable processes or with debris of fragmented processes were apparent. Other astrocytes showed swelling with short stubby processes. In Cat 1, outside of the hemorrhagic infiltration at about a distance of 0.5 mm., a few large hypertrophic astrocytes could be detected in the white matter.

The nerve cells in the zone of sponginess and pallor appeared to be relatively well preserved, although a few in the immediate vicinity of hemorrhagic infiltration re-

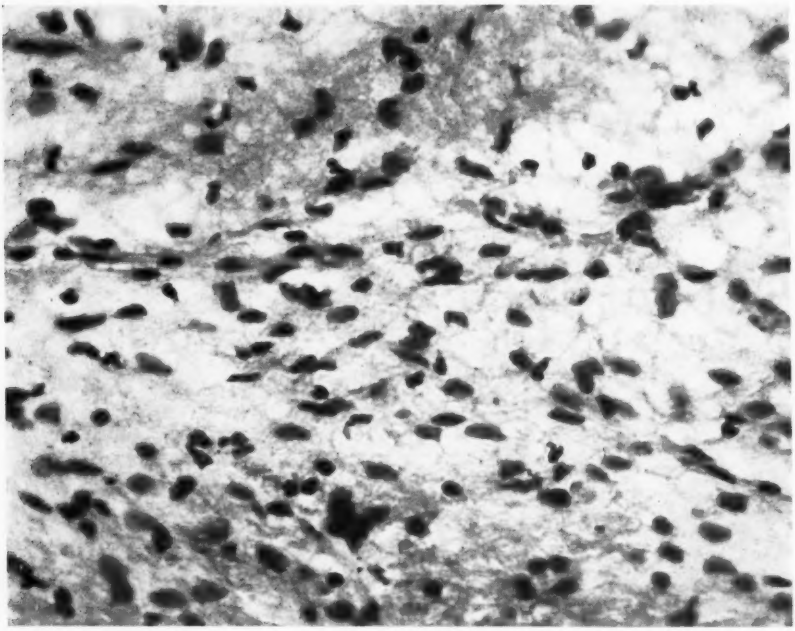

FIG. 2. *2½-hour stage.* Elongated, twisted microglial cells are seen in increased numbers in the brain tissue around the electrode track. Hematoxylin and eosin, ×440.

vealed a pale nucleus and chromatolysis. The axons of these neurons were swollen and fragmented.

In the gray matter, fragmentation, vacuolization, and globular formations of myelinated structures, and dust-like particles of myelin were observed. These changes were present within and for a short distance around the hemorrhages. In the white matter, irregular, small areas, measuring 0.5 mm. in extent, along the margin of the track revealed pallor of myelin with loss of staining with hematoxylin dyes. Areas of finger-like demyelinization extended parallel to persisting myelinated structures. In other areas where the damage was not so severe, the myelinated structures showed changes similar to those in the gray matter.

The endothelia of some vessels were slightly swollen. Around the vessels only polymorphonuclear leucocytes or their debris were present. Vascular proliferation, budding of capillaries, lymphocytes, mononuclear cells, plasma cells, and gitter cells were not seen. Fat could not be detected with the Sudan IV technique. Holzer stain failed to reveal any glial fibers.

3-Day Stage (Cat 3). The shape of the track was essentially similar to that described above although it contained less necrotic debris and only occasional red cells. The margin of the track revealed irregular areas of necrosis, extending in some parts 0.2–0.3 mm. into the area of sponginess and pallor, which measured 0.5 mm. in its greatest extent. In the necrotic areas some hemorrhages were seen. Only a few scattered polymorphonuclear leucocytes remained. There was evidence of proliferation of capillaries with swelling and budding of the endothelia.

There was a striking increase and extension of the microglial reaction for a distance approximately 1 mm. from the margin of the track. The microglial reaction was equally extensive in the gray and white matter.

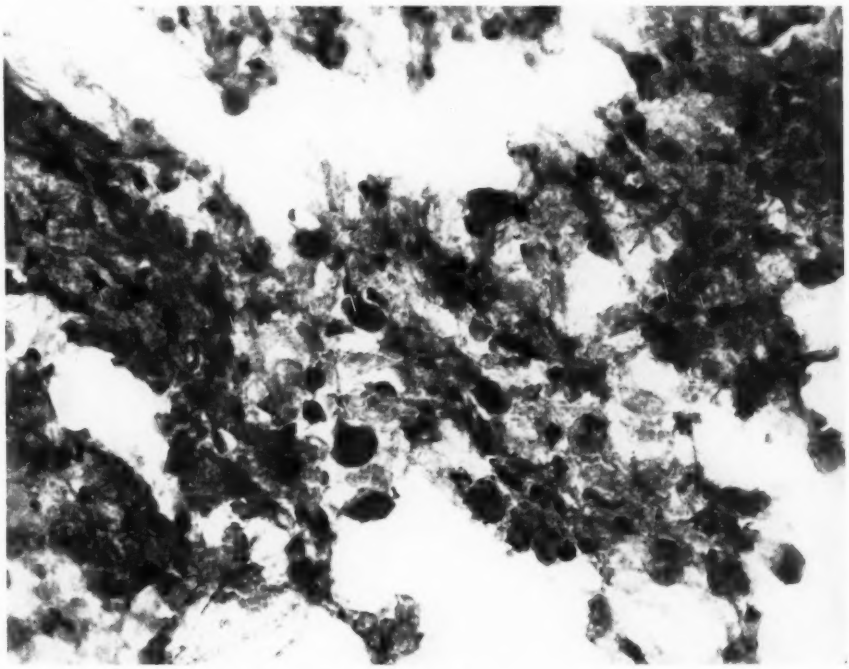

FIG. 3. *3-day stage.* Gitter cells phagocytizing the necrotic material around the electrode. Hematoxylin and eosin, ×440.

Within the necrotic areas gitter cells were present (Fig. 3). These were also seen in the area of pallor and sponginess, and were more numerous in the white than in the gray matter.

Outside of the area of pallor and sponginess, in a thin zone measuring 0.1–0.2 mm., a few moderately swollen and hypertrophic astrocytes could be detected. Occasionally forms that appeared binucleated were observed. Within the zone of pallor and sponginess, some irregular and altered astrocytes as described in the 24-hour stage could be discerned.

Disintegration of myelin appeared in irregular areas along the track and corresponded to irregular areas of necrosis. In the white matter in areas of demyelinization, gitter cells phagocytizing myelin debris were observed (Fig. 4); these were

absent in the zone of myelin breakdown in the gray matter. Fat stain revealed the presence of neutral fat within the gitter cells.

In the immediate vicinity of the track the nerve cells were necrotic. In the zone of sponginess and pallor the neurons were swollen. The meninges revealed some bleeding, extending 0.5 mm. at the point of entry of the electrodes, and the presence of a few mononuclear cells.

No lymphocytes, diffusely or perivascularly, were observed in the vicinity of the track. Holzer stain failed to reveal glial fibers.

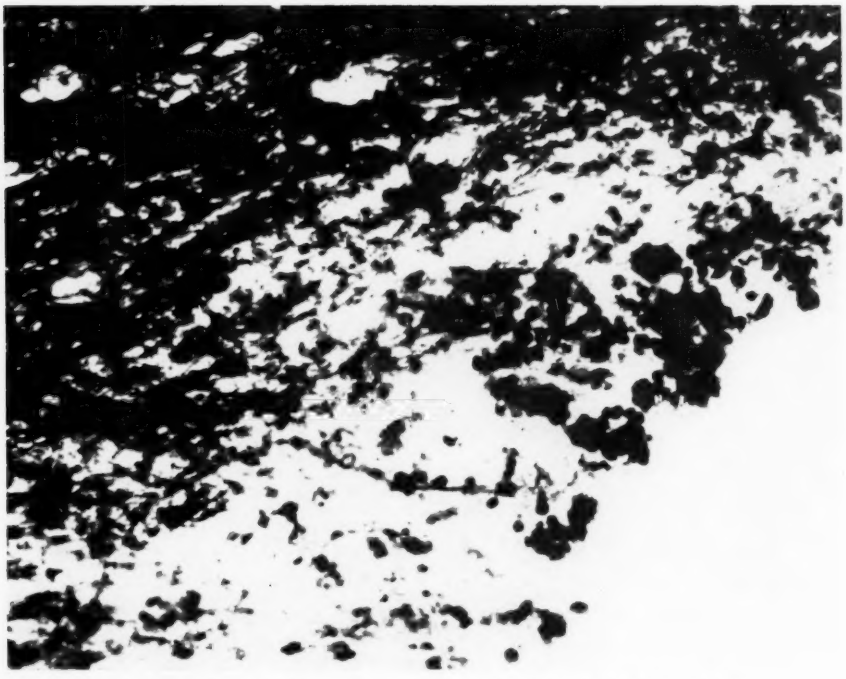

FIG. 4. *3-day stage.* Advanced myelin degeneration. Gitter cells phagocytizing myelin. Schroeder's myelin stain, ×440.

7-Day Stage (*Cats 5 and 6*). In the margin of the track, a marked proliferation of capillaries was obvious. This was somewhat irregular throughout the length of the track and measured approximately 0.1 mm. in width (Fig. 5). The proliferating capillaries seemed to occupy the areas of necrosis seen in the previous stages and the medial* margin of the area of pallor and sponginess. Elongated cells were seen streaming from and surrounding the vessels. Fibroblasts were present and in parts appeared in streaming aggregates. Between the budding capillaries, loose connective-tissue fibers could be detected.

Polymorphonuclear leucocytes were not seen. In Cat 6, a few round-cell infil-

* The terms medial and lateral are used in reference to the electrodes.

trates were seen perivascularly in the zone of proliferation of the capillaries. Surrounding this zone a well demarcated pale and spongy zone, measuring approximately 0.3 mm. in width, was observed.

The number of the gitter cells had slightly decreased as compared to the 3-day stage and they were present especially in the zone of capillary proliferation. Necrotic debris was still evident. The microglial reaction was similar to, but more prominent than, that in the 3-day stage, and extended into the surrounding zone of pallor and

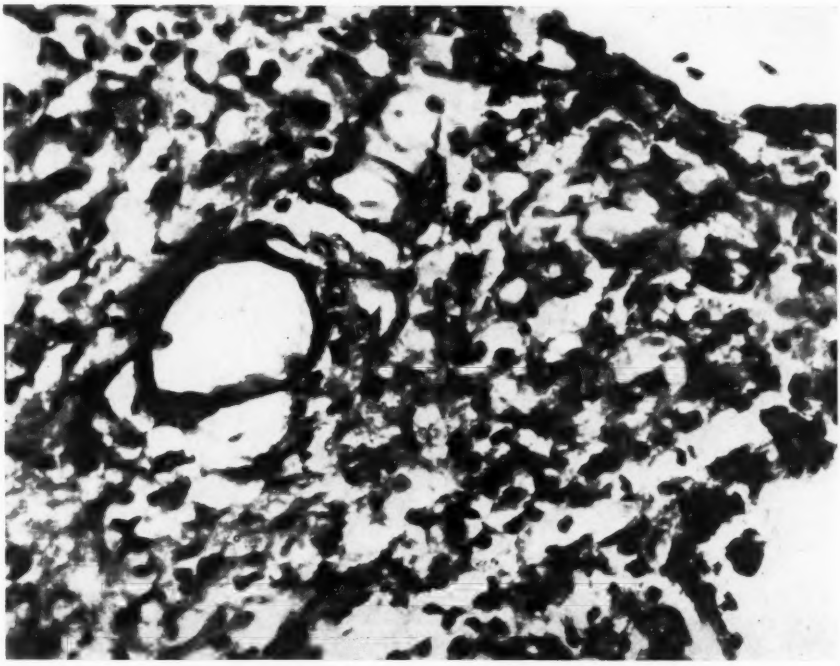

FIG. 5. *7-day stage.* Marked proliferation of capillaries and fibroblasts around the electrode track. Hematoxylin and eosin, ×440.

sponginess and into the apparently normal brain tissue for distances of 1–1.5 mm. from the margin of the track.

In the zone of pallor and sponginess, some swollen nerve cells revealing slight chromatolysis were observed. Some appeared to have undergone lysis and others were in stages of rhexis. Eccentric, irregular, pyknotic nuclei were observed in chromatolytic nerve cells. Among these degenerating forms, a few nerve cells appeared well preserved. In areas of neuronal degeneration, some of the nerve fibers revealed fragmentation, end-bulb formation and corkscrew-like appearances (Fig. 6). A few fibers revealed vacuolization along their course. Some fibers appeared well preserved although there was generally a decrease in fibers in such areas. These changes were present in an area 0.1–0.2 mm. from the margin of the track; beyond this the fibers appeared to be relatively well preserved.

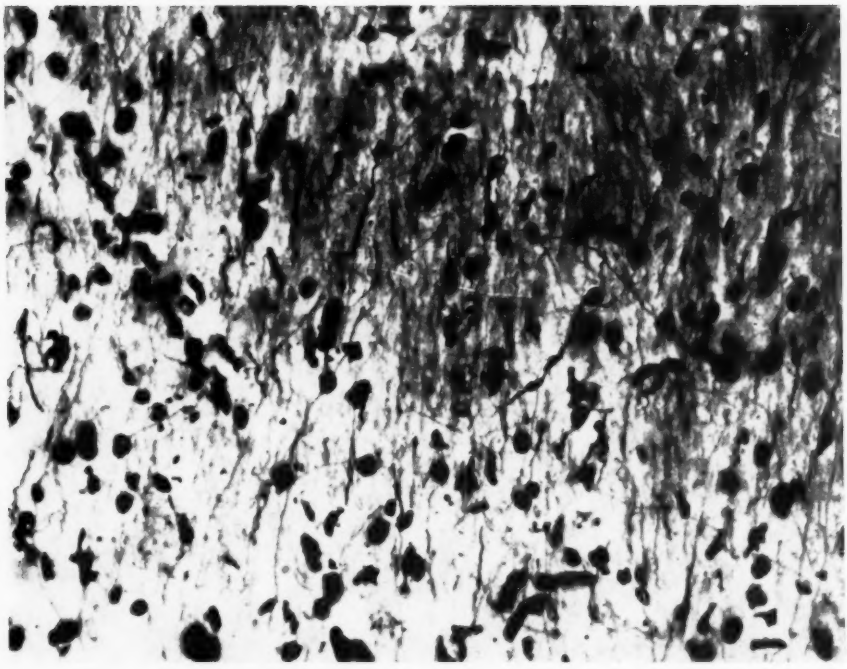

FIG. 6. *7-day stage.* Degeneration of neurofibrils in the vicinity of the electrode track. Triple impregnation, ×440.

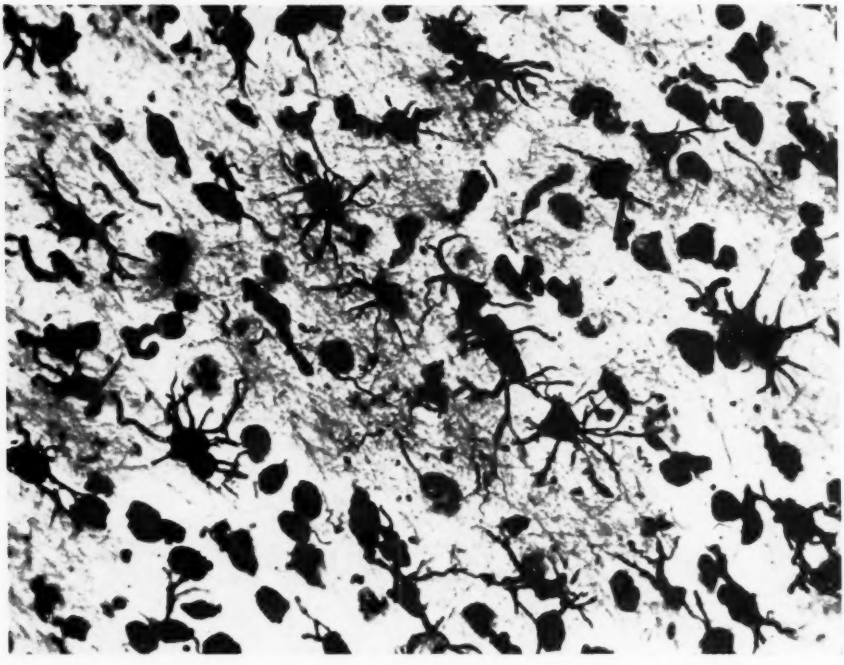

FIG. 7. *7-day stage.* Hypertrophic astrocytes in the preserved brain tissue lateral to the electrode track. Silver carbonate stain for astrocytes, ×440.

In this stage, a clear-cut zone of hypertrophic astrocytes was found (Fig. 7). The astrocytes appeared to be increased in number. Evidence of amitotic division was present. This zone started at a distance approximately 0.1–0.2 mm. from the margin of the track and extended for a distance of 1–1.5 mm. in width. A few regressive forms of astrocytes with small irregularly shaped nuclei and fragmented processes were seen in the zone of pallor. In those areas where the microglial reaction was most intense there were not so many astrocytes and vice versa. Holzer stain for the first time showed the presence of delicate glial fibers making their appearance in the

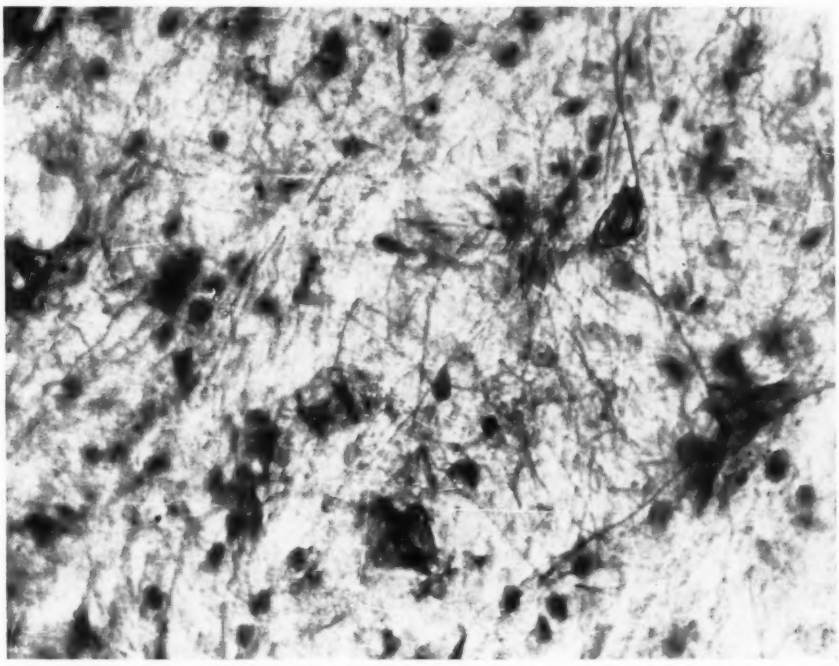

FIG. 8. *7-day stage.* Marked increase of glial fibers in the zone of proliferating astrocytes. Holzer's stain for glia fibers, ×440.

lateral portion of the pale and spongy zone and extending for a distance of 0.5 to 1 mm. (Fig. 8). They were more prominent in the boundary between this zone and the normal-appearing nervous tissue. In some areas only the fibers were stained, while in others the astrocytes were stained in addition. The glial fibers were more abundant in the white than in the gray matter.

Myelin stain showed a small irregular zone of demyelinization along the margin of the track which extended generally no more than 0.1 mm. (Fig. 9). In the gray matter, areas of complete demyelinization with minimal dust-like particles and rare gitter cells were seen. In the white matter, all stages of myelin degeneration could be seen. Here, as well as in the zone of capillary proliferation, gitter cells containing dust-like particles were present. Pouches of demyelinization running parallel to the well preserved myelin sheaths were again observed. Fat was stained in abundance along the margin of the track within gitter cells.

The meninges over the convexity in Cat 6 showed fibrosis and round-cell infiltration extending approximately 0.1 mm. from the portal of entry of the electrode.

15 Days (*Cats 7 and 8*). The proliferative changes of the capillaries and fibroblasts were very marked and came to occupy the immediate margins of the track. They formed a zone characterized by marked irregularities in width supplanting the zone of necrosis and the medial portions of the spongy and pale zone. Localized pouches of proliferating capillaries and fibroblasts were not rare. The fibroblasts were seen streaming in all directions although, in the immediate vicinity of the

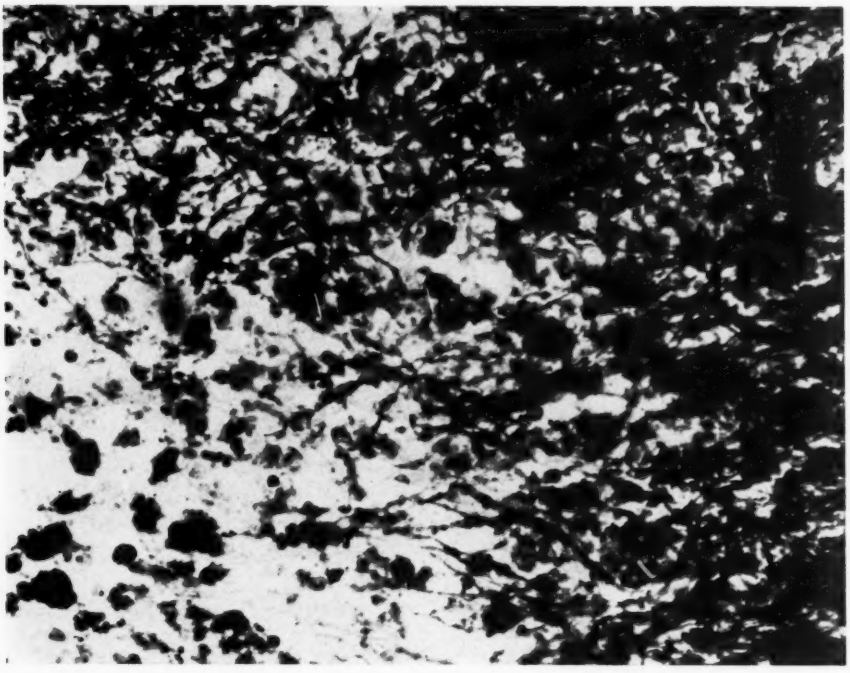

FIG. 9. *7-day stage.* Marked degeneration of myelin fibers and participation of gitter cells in the removal of myelin debris is seen. Schroeder's myelin stain, ×440.

track, they were found to run parallel to the track and to form a well defined wall separating the zone of capillary proliferation from the lumen of the track (Fig. 10). In some instances this wall was several cell layers thick. Collagenous fibers also ran parallel to and intermingled with the fibroblasts.

For the first time perivascular infiltrates composed predominantly of lymphocytes were found as a characteristic feature. They were present in the zone of capillary proliferation as well as in areas at distances of 0.5 mm. from this zone.

Intermingled with the lymphocytes, polymorphonuclear leucocytes were found and in some areas appeared in small aggregates.

The microglial proliferation and its distribution in gray and white matter was no different than in the previous stage. The zone designated as pale and spongy and the neuronal changes in these animals were similar to those described previously.

In the gray matter, hypertrophied reacting astrocytes were evident. These varied in intensity and extent, starting approximately 0.3–0.4 mm. from the margin of the track in the lateral portion of the zone of pallor, and gradually increasing to reach a maximum intensity at a region about 0.5 mm. from the margin of the track. They extended in a zone 1 to 1.5 mm. wide, diminishing in intensity as one proceeded laterally. Binucleated and multinucleated forms were seen. No particular arrangement of the astrocytes in relation to the margin of the track was seen. Areas surrounding the perivascular infiltrates were devoid of astrocytes. Some smaller and

FIG. 10. *15-day stage.* In the center of the picture the electrode track is seen. Fibroblasts and collagen are partially forming the wall. Hematoxylin and eosin, ×440.

altered astrocytes were seen occasionally in these regions. In those parts in which there was less perivascular infiltration, astrocytes seemed to approach the vessel more closely. In the white matter, the astrocytic reaction appeared less intense. The Holzer stain, however, showed intense staining of delicate fibers to the same extent described above in both the gray and white matter.

A complete area of demyelinization, measuring 0.1–0.2 mm., surrounded the margin of the track. Within the capillary zones many gitter cells, more than seen in previous stages, were packed closely together. Immediately surrounding this gitter-cell layer was a clear zone almost completely devoid of myelin and gitter cells (Fig. 11). In the boundary between the normal myelin and the clear zone, a very small transitional area of regressive myelin changes could be seen. In some areas there were pouch-like foci of demyelinization (Fig. 12). At times these extended 0.4–0.5 mm. from the margin of the track and formed finger-like extensions along and parallel to

the myelinated structures. Sudan stain demonstrated neutral fat within the gitter cells in the area immediately surrounding the margin of the track.

1-Month Stage (*Cats 9 and 10*). The prominent changes in this stage were the formation of a well defined capsule around the track and an increase of the astroglial response. In Cat 9 the electrode entered the cortex between two gyri, causing superficial, irregular, cortical lacerations before entering the subcortical white matter. Surrounding the superior portion of the track there were pouch-like areas of marked

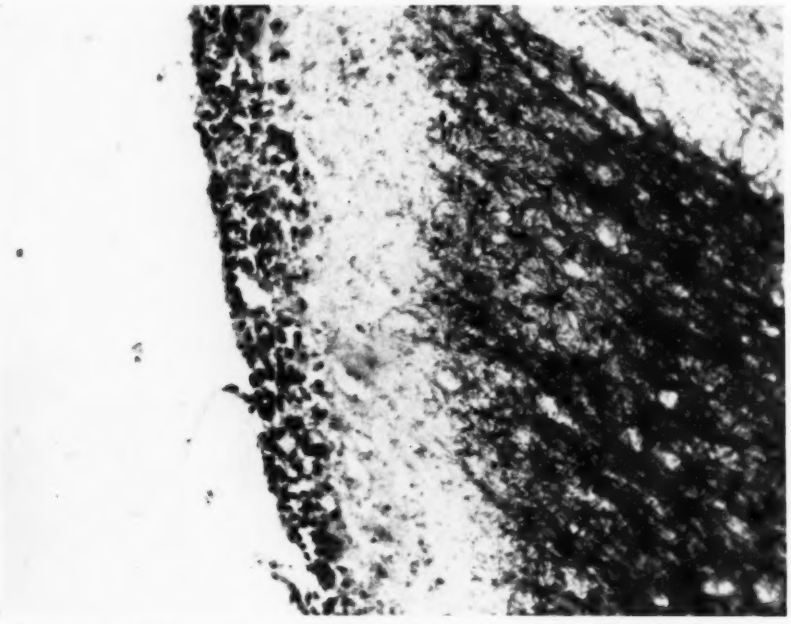

FIG. 11. *15-day stage.* At the left, the lumen of the electrode track is seen. Immediately to the right of it, a zone of gitter cells is present. The next zone, to the right, is almost entirely cleaned of myelin debris. Schroeder's myelin stain, ×440.

proliferaton of vessels and fibroblasts 0.5–0.7 mm. in extent. Here polymorphonuclear leucocytes and lymphocytes were present, the latter predominating. Surrounding these pouches was a zone of pallor and sponginess measuring 0.2–0.3 mm. in extent. As one followed the track down through the subcortical white matter to the caudate nucleus a definite capsule, composed of collagen and fibroblasts, 3–4 cells in width, was evident. Immediately surrounding this capsule was a thin layer of loose connective tissue. A few proliferating capillaries were present here and extended occasionally as pouch-like formations into the surrounding tissue. Polymorphonuclear leucocytes and gitter cells were confined to the areas of persisting capillary proliferation and were not seen in the inferior portion of the track.

The microglial reaction was still in evidence, reaching its maximum in the pouches of proliferating capillaries in the cortical gray matter. In the caudate nucleus it was not so intense and extensive.

Cat 10 showed the same evidence of encapsulation throughout the margin of the track and in most parts the capsule seemed to have replaced the zone of capillary proliferation. Pouch-like areas, 0.2–0.1 mm. in extent, were found irregularly along the track. The microglial reaction was less extensive than in Cat 9. Lymphocytes were present and polymorphonuclear leucocytes were absent.

Perivascular infiltrates and proliferation of fixed elements were noted occasion-

FIG. 12. *15-day stage.* Pouch of demyelinization next to the electrode track. Schroeder's myelin stain, ×440.

ally outside the capsule. In some instances the infiltrates were not confined to the Virchow-Robin spaces.

Generally in both animals the debris was markedly reduced, the tracks appeared better encapsulated and the brain tissue was devoid of nerve cells for a distance of 0.1–0.2 mm. around the track. A few remaining nerve cells showed pyknosis of the nucleus and vacuolization of the cytoplasm.

The astrocytes in both animals appeared increased over previous stages (Fig. 13) and formed a boundary immediately surrounding the capsule. Although these reacting cells were of greatest intensity just outside the capsule they extended for varying distances, 3 mm. in the cortex and 1.5 mm. in the caudate, in diminishing

intensity as one proceeded laterally. The processes of the hypertrophic astrocytes appeared to intermingle and form a glial meshwork. Holzer stain revealed an intense collection of glial fibers in the area surrounding the capsule which extended as much as 2–3 mm. from the capsule in decreasing intensity. These fibers appeared considerably increased around zones of persisting capillary proliferation. Generally the astrocytic reaction appeared greater in the gray than in the white matter. The astrocytes again showed no particular arrangement in relation to the wall of the track.

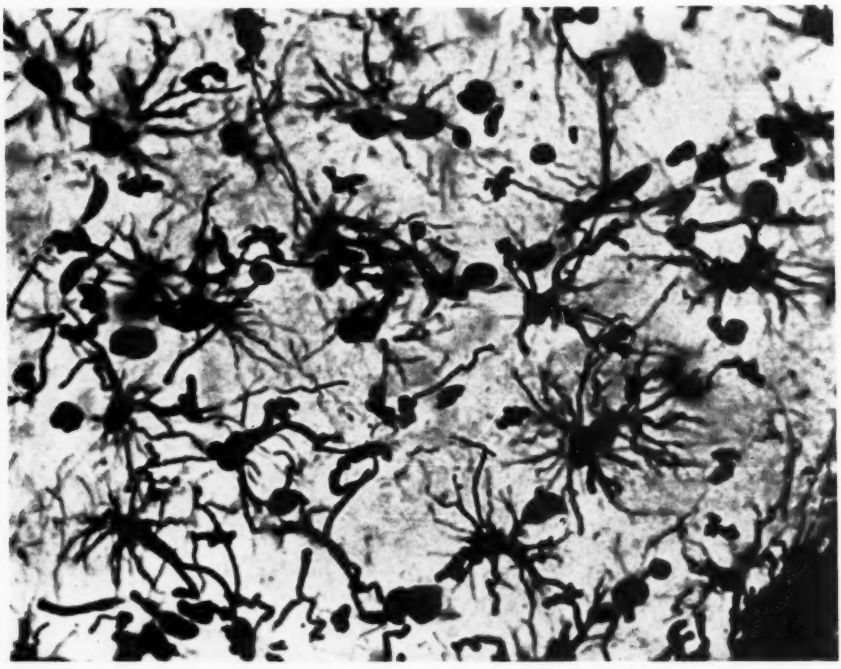

FIG. 13. *1-month stage.* Some binucleated and hypertrophic astrocytes as seen in the boundary surrounding the capsule. Silver carbonate stain for astrocytes, ×440.

Irregular areas of demyelinization were found along the margin of the track extending irregularly in some areas 0.2–0.3 mm. and in others 0.5 mm. All stages of myelin disintegration and removal were seen. Gitter cells were found transporting debris to the vessels. Some areas showed normal-appearing myelin extending to the capsule. Fat could be seen and in general was limited to those areas in which infiltrates prevailed.

2-Month Stage (*Cats 11 and 12*). This stage was characterized by a predominantly fibroblastic response and a definite progression in the formation of the capsule surrounding the track. The track was completely lined by a capsule composed of fibroblasts and collagenous tissue. In most areas, this was approximately 4 cell layers thick. The fibrous capsule had completely replaced the previously described zone of proliferating capillaries. Surrounding this capsule was an irregular zone of loosely

formed connective tissue averaging 0.1 mm. in width. In places, the connective tissue appeared narrower, and in others seemed to pouch into the surrounding tissue for 0.2 mm. In the out-pouchings, gitter cells were found occasionally. Within these areas pyknotic cells were observed and collapsed capillaries were evident. However, around some vessels, relatively well preserved lymphocytes persisted in Cat 12. Fibroblasts within the capsule and the surrounding connective tissue revealed pyknosis and stages of disintegration. Around the capsule complete absence of nerve cells was observed. However, nerve cells immediately beyond appeared well preserved.

A prominent feature at this stage was a marked decrease in microglia. These cells were in moderate numbers and many were small, irregular and pyknotic. It was still noted that these cells extended for 0.5 mm. from the margin of the track. In general there seemed to be a decrease in cellular elements as one proceeded laterally from the margin of the track.

Although many astrocytic cell bodies could be visualized, many of them appeared pyknotic and in various stages of disintegration. Nevertheless large, hypertrophic astrocytes were found concentrated in a zone surrounding the capsule. This zone was not so wide as in the previous stage. There was definite evidence that the processes of the astrocytes were thicker and the cell bodies stubbier. No significant difference between astrocytes in white and gray matter could be detected. Holzer stain revealed a marked increase of delicate glial fibers. These appeared most dense in the vicinity of the loose connective tissue just around the capsule and were intertwined with coarser fibers of collagen. This dense zone extended for about 0.1 mm. but in parts appeared to extend for 0.2–0.3 mm. In many areas in the white matter the glial fibers appeared arranged parallel to the myelinated fibers.

Myelin stain revealed irregular areas of demyelinization. In some areas there was almost a complete absence of myelin debris. Again, pouched-out areas 0.5 mm. in width were observed. In some areas the myelinated structures approached the capsule closely. Here the fibers were noted to end in club-shaped bulbs, appeared swollen and stained well with hematoxylin. In the white matter of Cat 12, the myelinated fibers which approached the capsule obliquely changed their course and ran parallel to the capsule towards the convexity of the brain (Fig. 14). It was further noted that the demyelinization tended to widen as the electrode entered from the meninges into the cortex, and from the ependyma into the caudate nucleus, producing wedge-shaped areas of demylinization at these points. Sudan stain for fat was negative.

4-Month Stage (*Cat 13*). This stage revealed a well formed connective-tissue capsule supported and reinforced by a layer of glial fibers. The capsule appeared thicker and dense fibers of collagen were much in evidence. The previously described area of loose connective tissue was now appearing in the stage of incorporation into the parallel-running fibers lining the track. Many coarse fibers of collagen were running parallel to the track in the more medial portion and were scattered somewhat haphazardly in the lateral portion. The thickness of the connective tissue surrounding the capsule varied. In most areas this measured 0.05–0.06 mm., and in some pouches, which appeared more cellular, extended for 0.1 mm. The number of fibroblasts was somewhat decreased and many of those present appeared pyknotic. Occasional foreign-body giant cells and hyalin-like material appeared in the immediate vicinity of the track.

The microglial cells were markedly decreased in number and some were pyk-

notic. Gitter cells with neutral fat were rarely seen, and perivascular infiltrates were absent.

Although a dense zone of astrocytes was noted around the capsule, the cell bodies appeared irregular and had diminished in numbers. The width of this zone varied and in some areas extended 0.1 to 0.2 mm. from the capsule. The glial fibers were short and thick, especially in the immediate vicinity of the capsule, becoming somewhat more delicate as one proceeded laterally. They did not appear in any particular

FIG. 14. *2-month stage.* Myelinated fibers are changing their polarity as they approach the electrode track (center). Schroeder's myelin stain, ×440.

arrangement in relation to the track. Glial fibers were more prominent in the caudate nucleus and cortex, although isolated areas were also intensely involved.

Irregular areas of demyelinization were present along the track and pouches of demyelinization extending 0.2 mm. were seen. In many areas myelinated fibers approached the capsule closely and in some instances changes of polarity of these structures and thickened end bulbs, as described in the 2-month stage, were seen. Also, the widened areas of wedge-shaped demyelinization, as the track entered from the meninges into the cortex and from the ependyma into the caudate, were noted again. In one area where the track interrupted the ependyma of the lateral ventricle as it passed ventrally into the caudate nucleus, streaming fibroblasts and collagenous fibers were found traversing the ventricle and connecting its dorsal and ventral wall.

6-Month Stage (*Cats 15 and 16*). The formation of the capsule in this stage did not show any significant difference from the previous stage. In those areas where it

was well formed, there was little loose connective tissue surrounding it and it seemed that most of this had now become incorporated into the wall of the capsule. Some persisting debris and gitter cells remained. Macrophages containing hemosiderin were seen occasionally along the capsule. A few pouches showing cellular activity persisted. In Cat 16 some contained microglia, lymphocytes, and proliferating connective-tissue cells. Others contained gitter cells and polymorphonuclear leucocytes. These pouches often gave a positive fat stain. In Cat 15, a relatively wide (0.1 mm.) wedge-shaped area was found as the track entered the corpus callosum. Here fibroblasts, gitter cells and microglia were seen. Sudan stain demonstrated fat within gitter cells. Myelin stain demonstrated all stages of myelin breakdown in persisting fibers.

Otherwise, the general myelin and glial changes did not differ significantly from those of the 2- and 4-month stage.

COMMENT AND DISCUSSION

In this study on the microscopic changes that ensue following the implantation of an electrode into the brain of animals, several changes characterized by stages of destruction, reaction and repair have become evident. These stages might profitably be discussed and compared with those changes reported following puncture wounds.

The most prominent finding in the 24-hour stage was an irregular hemorrhagic necrosis of the tissue traversed by the electrode. Infiltrations of this hemorrhage were found to extend into the surrounding brain tissue irregularly. Damage of local vascular patterns was undoubtedly a prominent factor in this irregularity. However, the fact that this central hemorrhage and infiltration appeared to be at a maximum in the superior portion of the track and to decrease progressively as one proceeded inferiorly, seemed to indicate that the insertion of the electrode might play a significant role. This is supported by the fact that the superior portion is traversed by a greater portion of the electrode and subjected consequently to more trauma. Other factors undoubtedly exist and will be discussed with patterns produced in later stages.

The pattern of the hemorrhagic infiltrations was also found to be characterized by a special relation to the myelin fibers. These infiltrations were found to follow paths seemingly of least resistance, parallel rather than perpendicular to these structures. Demyelinization proceeding in this pattern was seen in practically all stages. Thus it seems that the influence of preexisting structures is a local factor which determines to some extent the spread of hemorrhage and destruction. This initial pattern of hemorrhagic destruction has been discussed in some detail because it is upon this pattern that the subsequent pattern of reaction and repair is formed. This central necrosis has been observed by other investigators of puncture wounds in both human and animal material.[1,15,19,24]

Surrounding the necrosis, an area of edema was evident characterized by sponginess and pallor of this tissue. This was irregular in width along the track and seemed to vary in direct proportion to the amount of hemorrhage

present locally. Morphological changes indicating ischemia, as were seen around traumatic hemorrhages in humans,[22] were not observed in our experimental material.

In the medial zone of edema regressive changes of all the elements were seen. These changes did not differ from those found in the central hemorrhagic portions and were similar to alterations around human puncture wounds of 24 hours' duration or less.[1]

As one proceeded laterally to the margin of seemingly normal tissue the changes became less severe. The intensity of changes would seem to be exerted on structures situated next to the hemorrhage.

The main reacting cells in this early stage were predominantly the polymorphonuclear leucocytes and the microglia. The participation of polymorphonuclear leucocytes varied and was more prominent in areas of hemorrhagic destruction and debris. Early evidence of phagocytosis was observed as necrotic debris within the cytoplasm of these cells. It was interesting to observe the proliferation of microglial cells without evidence of vascular mesenchymal proliferation and in the absence of perivascular infiltrates, indicating that these cells were derived from the pre-existing microglial elements. These cells were not limited to the necrotic zone but were found in brain tissue apparently not involved by necrosis or edema. Gitter cells and microglia in stages transitional to these were not observed in this early stage. Similar observations were reported in the human after ventricular punctures.[1] Our results did not support observations of del Río-Hortega[24] who found typical gitter cells in experimental wounds in cats 24 hours after puncture of the brain.

In the animal sacrificed after 3 days an irregular area of necrosis lined the track once again, although this was apparently decreased in width, and hemorrhage and debris were less evident. Apparently the medial portion of this edematous zone was being incorporated into the necrotic portion. It is known that severe edema may cause complete necrosis of the tissue, especially of the myelinated structures.[14]

The microglial reaction was increased over the 24-hour stage, and gitter cells made their appearance for the first time. This is in agreement with observations of other investigators on histological changes following puncture wounds in humans and animals.[1,15,24] Transitional forms from microglia to gitter cells as reported by others[15,24] were not detected in our material. It was noted that these phagocytic cells were present in the area of necrosis in the white matter and rarely in the gray, although extensive areas of hemorrhagic necrosis were found in both. The extent of breakdown of red cells was equal in both areas. Destruction of myelin, however, was of greater concentration in the white matter, probably because of a greater degree of sensitivity of these structures to edema and extravasates. It is conceivable from this observation that the initial stimulation to the formation of compound granular corpuscles is related to the degree of destruction of myelin, and not to the extent of breakdown of red cells as reported.[21]

The polymorphonuclear cells had largely disappeared by this stage. This is in disagreement with observations made by others[1] that these cells were more numerous than gitter cells 3 days after ventricular puncture in humans.

Medial to the zone of necrosis, proliferative vascular changes characterized by budding of the endothelia were observed. These changes were seen for the first time on the 4th day in ventricular puncture wounds in humans.[1]

There was a moderate number of hypertrophied astrocytes forming a boundary between the zone of edema and the apparently uninvolved tissue. Binucleate forms were seen, although it could not be ascertained whether amitotic division was taking place. The white and gray matter showed no significant differences in the appearance of these cells. Reaction of the astrocytes was observed 4 days after puncture wounds in humans[1] and in rabbits 3 days[15] and 4 days[25] after the initial trauma.

In the animals sacrificed after 7 days, an increase of the proliferation of capillaries had taken place. Similar proliferation of the capillaries has been reported 5 to 7 days following puncture wounds in humans.[1] Streaming aggregates of fibroblasts and some collagenous fibers were first observed in this stage. Elongated cells in apparent transition to microglia were identified streaming from the walls of the vessels into the surrounding brain tissue. Round-cell infiltrates were seen for the first time perivascularly. Polymorphonuclear leucocytes were not found. Baggenstoss *et al.*[1] have described an abundance of polymorphonuclear leucocytes active in phagocytosis in this stage, and also the presence of lymphocytes. Transitional forms from microglial cells to fully formed gitter cells could be seen at this stage. These were reported 6 days after stab wounds in rabbits.[15,25] The observations of cellular transitional forms between lymphocytes and compound granular corpuscles reported 8–10 days in puncture wounds in humans[1] could not be confirmed.

The necrotic debris appeared to be somewhat decreased over previous stages, although irregular pouches in which hemorrhages, abundant debris, and various stages of demyelinization were present, were noted along the track. These probably represented areas of initially more extensive involvement.

The zone of hypertrophied astrocytes had increased in width and there were more binucleate and multinucleate forms. Amitotic division was in evidence. Generally speaking, where intense microglial reaction was observed, the response of astrocytes was moderate and vice versa. A zone of astrocytic proliferation has been reported in both human and animal material 5 to 7 days after puncture wounds.[1,15,25,32] del Río-Hortega and Penfield[25] reported amitotic division. The same investigators have reported some tendency to radial arrangement of the astrocytes about the wound 6 days after trocar stab wounds in rabbits. Such a finding was not detected at this stage of this study. Rand and Courville,[21,22] in an extensive study of the neuroglial findings surrounding contusions and lacerations in human ma-

terial, and in a review of such changes in the experimental material of other investigators, have summarized the changes that neuroglia undergo as follows: Immediately surrounding the central zone of destruction, there appears a zone in which the neuroglia undergo complete regressive changes from which they are incapable of recovering and are ultimately incorporated into the central zone, which they have termed the "zone of complete regressive stage." Outside this zone, a variable zone appears in which neuroglia undergo regressive changes from which some may be capable of recovering, while others go on to complete regression. They have termed this zone the "zone of reversible reaction" (Penfield's "reversible reaction"). Lateral to this zone, there appears the "zone of reaction" in which the neuroglia undergo hypertrophy and proliferation. Stages in the formation of these zones have been confirmed at this and previous stages of this study.

In the animals sacrificed after 15 days, the zone of capillary proliferation had replaced, for the most part, the necrotic zone. Circumscribed wider foci of capillary proliferations along the track were evident.

A prominent feature of this experimental stage was the apparent vigor displayed in the connective-tissue reaction. Fibroblasts in medial portions were found directed radially toward the margins of the track where in some areas they ran parallel to the track, forming a wall, several cells wide, separating the margin from the lumen. Collagenous fibers were similarly increased in this region. Baggenstoss *et al.*[1] found a similar zone of proliferating capillaries and fibroblasts 12 to 14 days after ventricular puncture wounds in humans. However, these investigators reported that this zone had largely replaced the zone of edema and that the capillary and fibroblastic reaction was observed to be more vigorous in the cortex than in the white matter. Such observations were not made at this stage of this study. Penfield and Buckley[19] reported that the vascular reaction was as marked in the white as in the gray matter in early stages of trocar stab wounds in dogs. In general, in our study the capillary and fibroblastic reaction was found to be more vigorous where irregular extensive necrosis was present, whether in the white or in the gray matter.

The zone of edema persisted at this stage and did not differ significantly in width from the previous stage. Gitter cells had largely removed the necrotic debris and were found to be increased in number in the zone of capillary proliferation, apparently in the stage of transporting this debris to the capillary spaces. Similar observations have been reported in ventricular wounds in humans after 12 to 14 days.[1] Surrounding this zone of capillary proliferation was a clear zone almost completely free of myelin debris and phagocytes. At the margins of this zone, near the normal-staining myelin, active regressive changes were found to persist in the ends of the myelinated fibers, and compound granular corpuscles were evident here. Rand and Courville[23] have reported these regressive myelin changes around the "clear zone" in lacerations of the brain and have found them to persist for many months, leading to a slowly progressive widening of the zone of demyelinization.

Mononuclear perivascular infiltrates appeared prominently in this stage. Similar observations have been made 12 to 14 days following ventricular puncture wounds in humans.[1] The reappearance of polymorphonuclear leucocytes was noted in this stage. They appeared in well defined localized masses in the central zone of capillary proliferation and rarely in the zone of edema. No evidence of contamination was found. It could be that additional and more recent bleeding from the proliferating capillaries was the cause of this leucocytic reaction. Baggenstoss *et al.*[1] reported polymorphonuclear cells persisting, though decreased in number, 12 to 14 days following puncture wounds in humans. The microglial reaction did not differ significantly from that of the previous stage.

The zone of hypertrophied astrocytes persisted in the lateral zone of edema and formed a diffuse boundary here. Some astrocytes had undergone the reversible astrocytic reaction described by others.[21,22] The regions surrounding perivascular infiltrates were either devoid of astrocytes or contained regressive forms. It was interesting to note at this stage that the astrocytic reaction was generally more marked in the gray than in the white matter. This difference in the intensity of reaction could not be explained on the basis of irregular traumatic involvement since localized extensive areas of involvement in the white matter showed a less intense response than areas not so extensively involved in the gray. Penfield and Buckley[19] have reported less extensive gliosis in the white matter following trocar and cannula stab wounds in dogs. Radial arrangement of the astrocytes about the wound as reported by several investigators[15,19,25] was not observed at any stage of this study. In those portions in which any particular arrangement was noted, the fibers of the astrocytes as seen in Holzer stain seemed to be arranged parallel to the myelinated structures.

In the animals sacrificed after 1 month, the irregular involvement of areas along the track by the initial hemorrhagic necrosis, as described previously, was evidenced by all stages of reaction and repair. Necrotic debris was essentially absent from these regions. Myelinated structures approached the capsule closely and changes in the myelin at the margin were rare. Gitter cells were not observed. A zone of edema surrounding these regions did not exist. A microglial reaction persisted though it was milder than in other areas to be discussed. On the other hand, in some areas along the margin of the electrode track, the repair had not progressed so far. These stages of delayed repair undoubtedly were related to the patterns of initial traumatic necrosis that have been described. Areas of greatest reaction were generally situated in the more superior portions of the track.

The astroglial reaction appeared greatly increased over previous stages. In those areas in which the connective-tissue capsule was well formed an increased number of swollen astroglia, with fine processes, approached the margin of the capsule closely and appeared in greatest intensity there. Similar observations have been reported by del Río-Hortega and Penfield.[25] Linell[15] noted this moving of the astrocytes to the margin of the wound 21 days after puncture wounds in rabbits. He found a marked reduction of the

numbers of reacting astrocytes at the margin 28 days after the initial trauma. del Río-Hortega and Penfield[25] have observed that the hypertrophic neuroglia occupied an area smaller than initially, 19 days after puncture wounds in rabbits. These observations were not noted at this stage in our material. On the other hand, Baggenstoss *et al.*[1] reported no other change of the astrocytic reaction than a hypertrophy of the cells 19 to 25 days after puncture wounds in humans.

The animals sacrificed 2, 4 and 6 months after the implantation of the electrodes revealed stages of advanced repair and scar-tissue formation. The most striking morphological feature in these animals was the tendency to encapsulate completely the implanted electrode. The capillaries were collapsed in most areas along the margin of the electrode track.

The connective tissue revealed the following changes: The number of fibroblasts was decreased and there were definite signs of regressive changes, like pyknosis, in the persisting cells. Associated with these changes was a definite increase of the collagenous fibers. These were more numerous in the immediate vicinity of the track as compared to the zone occupied by the loosely formed connective tissue. The perivascular infiltrates encountered in previous stages were absent. The few still present revealed regressive changes of the lymphocytes.

At this stage of the reaction, which one may generally call the stage of cellular regression and of fiber formation, the microglial cells also revealed a tendency to disappear. The same is true concerning the astrocytes, which were decreased in numbers and showed definite regressive forms. The cellular elements were decreasing, and the fibers, collagenous and glial, dominated the morphologic changes.

Glial fibers intermingled with the collagenous fibers; they reinforced the scar tissue formed around the electrode track and affixed the surrounding brain tissue to the fibrous capsule. As we have already described, the pre-existing structures (myelin) had an influence upon the development of certain acute phenomena such as bleeding, edema and demyelinization. The same is true for the gliosis. Thus the glial fibers were found to run parallel to the pre-existing myelinated structures.

Only occasionally, especially in those areas referred to previously as pouch-like areas, a few gitter cells and degenerative changes of myelin were still evident. For the most part, however, the myelinated structures interrupted by the implanted electrode were found to be thick and stained well with hematoxylin dyes. Some of the myelinated fibers appeared to change their perpendicular polarity and to run for short distances parallel to the connective-tissue capsule. These phenomena may be interpreted as slight abortive attempts at regeneration. The use of silver techniques did not clarify the structural changes to allow more positive conclusions about regeneration. Recent review of the literature and experimental work indicates that stages of neuronal regeneration may occur in mammals.[4]

Only in a few regions around the track, described previously as outpouchings, did cellular elements, like fibroblasts, gitter cells and lympho-

cytes, persist. For this persistence, the explanation offered in the initial stages may be reemphasized; namely, that these areas represent structures bearing the brunt of the initial trauma. Another contributory factor for the persistence of that phenomenon may be the fixation of the brain tissue in the less flexible capsule around the electrode.

In similarly oriented experiments in the literature, the following findings have been detected in late stages corresponding to the 2-, 4-, and 6-month animals: Linell[15] has found concentration of the glial fibers at the margin of the wound, and a decrease in the astrocytic cell bodies 62 days after trocar stab wounds in rabbits. del Río-Hortega and Penfield[25] found similar changes, in late stages, in rabbits sacrificed at intervals up to 73 days after trocar wounds. They described a heavy central connective-tissue core with a surrounding concentration of astrocytes bearing processes arranged radially about the track. These investigators reported a contraction of this glial-mesenchymal scar with distortion of the surrounding brain tissue. Similarly, Penfield and Buckley[19] have described these same phenomena in late stages following trocar stab wounds in dogs. All above-mentioned findings are in general agreement with observations made during the present study with the exception of the radial arrangement of the astrocytes. Furthermore, as in our experimental material, del Río-Hortega and Penfield,[25] in trocar stab wounds in rabbits, found activity of gitter cells. It has been reported in human puncture wounds[1] that foci of necrosis are present in later stages.

During this experiment, regional differences in damage, removal, and repair were found. Partially, these differences are ascribable to the initial trauma and the influence of preserved structures upon the spreading of the damage. In this connection, it is worth mentioning that through all stages of this experiment, wedge-shaped areas of necrosis and demyelinization were found in the nervous tissue immediately below the meninges and the ependyma. It could well be that limiting membranes (meninges, membrana limitans superficialis, and ependyma) lying on surfaces of the brain caused an increased resistance to the entering electrode and indirectly more pressure on the underlying nervous tissue.

In the later stages of the experiment foreign body giant cells were found. These probably originated from material used in the construction of the electrode.

The several stages of discussion indicate that variations in the extent of damage and repair exist in the nervous tissue around the electrode. Statements made by investigators about "mild" or "moderate" gliosis and expressed in millimeters about the electrode track are at least over-simplifications of the existing situation. One cannot always predict what damage an electrode may cause, as indicated by variations found within and between stages of this experiment.

SUMMARY

A timed experiment was undertaken to investigate the changes caused by implanted electrodes in the brain tissue of cats.

Fourteen animals were sacrificed and their brains were examined histo-

logically at intervals of 24 hours, 3 days, 7 days, 15 days, 1 month, 2 months, 4 months, and 6 months after implantation of the electrodes.

The following changes were detected:

1. *24 hours*—This stage was characterized by hemorrhagic necrosis extending irregularly into the tissue surrounding the track, and the participation of polymorphonuclear leucocytes in the tissue response. Activation and proliferation of microglial cells was observed.

2. *3 days*—The polymorphonyclear leucocytes were decreased in number and the microglial cells were proliferating more actively. Phagocytic activity and the formation of gitter cells were seen for the first time. Proliferating capillaries were observed. Several stages of demyelinization were described. A mild reaction of the astrocytes was initiated.

3. *7 days*—This stage was characterized by an increase of the mesenchymal reaction and marked proliferation of the capillaries. The necrotic zone decreased considerably. Streaming fibroblasts around the implanted electrode and some collagenous fibers were observed. Round-cell infiltrates were seen for the first time perivascularly. Microglial cells were actively participating in the reaction around the electrode. The zone of hypertrophic astrocytes had increased in width.

In all these stages edema was a prominent morphologic feature.

4. *15 days*—Most of the necrotic zone was replaced by proliferating capillaries. The number of fibroblasts, as well as the collagenous fibers, was considerably increased. The zone of edema persisted. As in the previous stages, regressive neuronal changes were observed. Myelin debris was largely removed by gitter cells. An area free of myelin could be seen between the electrode track and the surrounding brain tissue. Reappearance of polymorphonuclear leucocytes was noted at this stage. Surrounding the zone of demyelinization was a zone of hypertrophic astrocytes.

5. *1 month*—The fibroblasts and collagenous fibers had largely replaced the zone of capillary proliferation and were forming a capsule around the electrode. Necrotic debris was essentially absent. The microglial response was generally milder than in previous stages. The astroglial reaction appeared greatly increased over previous stages.

6. *2, 4, and 6 months*—Advanced stages of repair and scar tissue formation were seen. There was an obvious tendency to encapsulate the implanted electrode. Regressive changes were observed in the capillaries, fibroblasts, perivascular infiltrates, microglia and astrocytes. Fibers, collagenous and glial as well, were concentrated around the electrode and were affixing the surrounding brain tissue to the fibrous capsule.

7. In all these stages, variations in damage, removal and repair of the brain tissue surrounding the electrode were found. Their significance was discussed in relation to the initial trauma and to the preserved pre-existing structures.

8. Regional differences in the involvement of different parts of the brain tissue were discussed and an attempt was made to explain their significance.

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CASE REPORTS

EPIDURAL HEMORRHAGE SECONDARY TO CAVERNOUS HEMANGIOMA OF THE PETROUS PORTION OF THE TEMPORAL BONE

LAIBE A. KESSLER, M.D., LOWELL G. LUBIC, M.D., AND YALE D. KOSKOFF, M.D.
Department of Neurosurgery, Montefiore Hospital, Pittsburgh, Pennsylvania

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Hemangiomas of the bone are rare. They constitute from 1 to 2 per cent of all bone tumors. The most common site of hemangiomas is in the vertebrae, those of the skull being second in frequency. In the skull they are usually found in the calvarium, involving the parietal and frontal lobes.[1,3] There are two types of hemangiomas. The capillary variety is made up of closely packed capillaries which are lined by a single layer of nearly cuboidal endothelial cells. The more common cavernous type is composed of larger blood-filled spaces which are lined by a single layer of flattened endothelial cells. Elastic fibers and smooth muscle are usually not present in the walls of these tumors and the amount and character of the fibrous supporting stroma vary greatly.[2]

CASE REPORT

An 8-year-old, white female was admitted to the Neurosurgical Service of the Montefiore Hospital on Feb. 9, 1956. The child had been in good health until 2 days previously, when she complained of an earache accompanied by a small amount of blood exuding from the canal of the right ear. This persisted for 24 hours, and a local physician was called. He noted injection of the right eardrum and prescribed penicillin. That evening the child vomited and felt chilled. On the morning of February 9 the mother could not arouse her. She was taken to another hospital where roentgenograms of the skull showed evidence of mastoiditis. The patient continued to be comatose and was transferred to the Montefiore Hospital that evening with the diagnosis of brain abscess. Past history for chronic ear infection was negative. There was no history of recent head trauma.

Examination. The patient was comatose, with a temperature of 101°F. rectally, a pulse rate of 106/min., and a respiratory rate of 20/min. The neck was supple. There was no cranial bruit. The right pupil was 5 mm. in diameter and fixed; the left pupil was 2 mm. and fixed. There were no gross extraocular muscle palsies. The optic discs were flat, and the corneal reflexes were absent. There was dried blood in the right ear canal with some injection of the drum. There was a left central facial paresis with a left hemiparesis; the deep tendon reflexes on the left side were 3 plus and slightly more active than those on the right. Plantar responses were extensor bilaterally.

Roentgenograms of the skull, including Towne views, revealed a loss of normal cellular structure in the base of the right petrous pyramid and also in the bone of the mastoid process itself. There was a smearing of the bony structure, indicating the presence of bone destruction. The roentgenologist felt that the above findings suggested an acute exacerbation of a chronic sclerosing mastoiditis. There was no evidence of skull fracture (Fig. 1).

The clinical impression was herniation of the medial portion of the temporal lobe into the tentorial notch with secondary compression of the right 3rd nerve and the brain stem. The cause of the herniation was not ascertained pre-operatively.

Operation. Upon opening the squamous portion of the right temporal bone, about 250 cc. of blood gushed out under pressure. The bony opening was enlarged, but no bleeding point

could be found. The dura mater was opened, but there was no evidence of subdural hematoma. The patient's condition remained poor, and she expired 24 hours following surgery.

Autopsy. There was a bluish discoloration of the right petrous pyramid. The bone was stripped away, and inside was found a large mass of friable vascular tissue. There was some partially organized and clotted blood over the dura mater in the floor of the middle cranial fossa and over the right parietal region. The sulci were shallow and the convolutions were flattened over the right cerebrum. There was moderate herniation of the uncus and hippocampal gyrus of the right temporal lobe. Focal hemorrhages measuring up to 0.5 cm. were

FIG. 1. Roentgenogram showing changes in right petrous pyramid and mastoid process (see text).

present in the inferior portion of the right parietal lobe. There were no gross hemorrhages noted on section of the brain stem.

Microscopic Examination. Sections of the cerebrum and brain stem showed generalized hyperemia and edema. There were numerous small focal hemorrhages and degeneration of the parenchymal tissue in the mid brain and the pons. Sections from the bone of the right petrous pyramid exhibited moderate to marked proliferation of distended and engorged small blood vessels. There was associated moderate extravascular hemorrhage. The pathologist felt that these findings were consistent with the diagnosis of cavernous hemangioma (Fig. 2).

COMMENT

The patient had a cavernous hemangioma in the right petrous pyramid which ruptured spontaneously, causing a secondary epidural hemorrhage and subsequent

FIG. 2. Photomicrograph of cavernous hemangioma of petrous pyramid.

death from uncal herniation with compression of the vital centers in the brain stem The probability is that this vascular tumor had been present since birth. Even in retrospect there was nothing in the roentgenograms to suggest the diagnosis of cavernous hemagioma. This case is documented because of its rare occurrence and with the hope that, in the future, earlier recognition of such a lesion may prevent a fatal outcome.

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HEMIBALLISMUS RELIEVED BY VENTRAL QUADRANT SECTION OF THE CERVICAL SPINAL CORD WITHOUT PARALYSIS*

RICHARD E. STRAIN, M.D., AND IRWIN PERLMUTTER, M.D.
University of Miami School of Medicine, Miami, Florida

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Hemiballismus, as you know, is a rare disorder in which violent, uncontrollable movements of one arm and leg occur. The term "hemiballismus," credited to Kussmaul by Oppenheim, is reserved for those cases in which the movements are massive, violent, flinging movements of one extremity or one half of the body. Walker[17] stated that hemiballismus probably should be considered a variety of choreo-athetosis. These involuntary actions may begin at times with little more than flinging of an article from the hand, but soon reach such dramatic violence that the patient may be thrown from the bed by them. The flingings and hurlings of the extremities usually persist through every waking moment. Although the movements disappear with sleep, sleep is usually impossible even with heavy sedation. The patient becomes distraught and eventually exhausted[9] by the violent constant movements and usually dies of pneumonia or cardiac failure in a few days to 5 weeks.

Greiff[5] in 1883 was the first to localize the lesion to the contralateral corpus subthalamicum. This was forgotten until Bonhoeffer[1] in 1897, Jakob in 1923 and Martin[10] in 1927 reverified the pathology to be in the contralateral subthalamic nucleus of Luys.

Moersch and Kernohan[13] in 1939 reported a case. Whittier[18] in 1947 was able to find 30 cases with adequate pathological studies of the subthalamic nucleus. In 6 of these the subthalamic nucleus was intact, but it was presumed that its connections were interrupted. In 4 cases no change was noted in the nucleus or its connections. Meyers *et al.*[12] believed that the lesion may arise in different areas of a neural circuit rather than be confined to the nucleus of Luys. In the majority of instances, the lesion is vascular, either hemorrhage or thrombosis, although occasional cases of neoplastic involvement have been reported.

Hampel[6] stated that the blood supply of the subthalamic nucleus is derived from three arteries—a branch of posterior cerebral, a choroidal artery and a branch of the posterior communicating. Carpenter[4] felt that the primary blood supply is from branches of the posterior cerebral artery.

The Vogts had expressed the belief that a topical relationship existed in the subthalamic nucleus. In the cases reviewed by Whittier[18] the oral pole was destroyed in 17, with the face being involved. Meyers *et al.*[12] have felt that there is a somatotopic localization in the nucleus with rostral lesions causing movement of the head and neck, lesions of the middle portion affecting the upper extremity and the caudal portion involving the lower extremity.

Herz and Meyers[7] proposed a theory for the pathogenesis of hemiballismus in which impulses of the kinetic circuit flow from the periphery to the thalamus and are passed on to the postcentral areas 1, 2, 3—then by U-fibers to the motor area 4 and 4Y and premotor area 6 (Fig. 1).

* Presented at meeting of the Harvey Cushing Society, Honolulu, Hawaii, April 17, 1956.

Kinetic impulses leave the motor cortex and pass by parapyramidal fibers through subcortical nucleus, probably including the reticular substance to the lower motor neurone—presumably some over extrapyramidal cord tracts. The kinetic circuit, when unopposed by a suppressor circuit, produces ballistic movements of the opposite half of the body.

The suppressor circuit S, which phasically complements and suppresses irregular showers of kinetic impulses, starts with impulses from the periphery via the thalamus going to the cortical suppressor strip 4S; from suppressor strip 4S impulses go via the

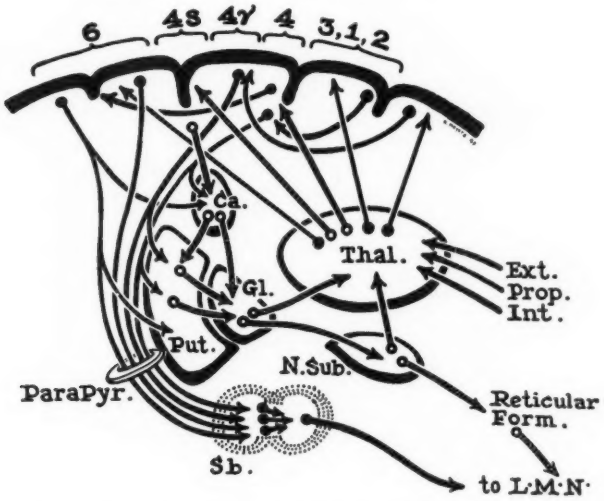

FIG. 5. A reverberating circuit theory of the pathogenesis of hemiballism.[12] Solid black line, kinetic circuit (*K*); black line with white dots, suppressor circuit (*S*). K circuit, acting unopposed, produces ballistic movements of the opposite half of the body; S circuit phasically complements and suppresses the irregular showers of kinetic impulses. Under normal circumstances, the latter are dissipated in such a way as to contribute to normal muscle tonus.

FIG. 1. Diagram reproduced from Baker's *Clinical Neurology* with the kind permission of E. Herz and R. Meyers[7] and P. B. Hoeber, Inc.

caudate, putamen, globus pallidus through the subthalamic nucleus to the reticular substance and finally the lower motor neurone. While these circuits are still highly theoretical, they appear to be compatible with known facts of hemiballismus.

Nearly all recent writers have emphasized that hemiballismus should be treated surgically by early operation if these patients are to survive.[11]

Clinically the majority of patients are elderly—the average age in Whittier's series was 64, although Bonhoeffer had a patient 7 years old.

As a rule the onset is sudden. Hypertension and arteriosclerosis are usually present, and the hypertension is usually of a formidable degree. Such individuals are not good surgical risks and yet procrastination in the hope that the violent movements will stop nearly always leads to the death of the patient.

The number of reported cases in which surgery was performed appears to be

small. Bucy[3] operated in 1 case and removed areas 4 and 6 with success. Meyers *et al.*[12] reported 2 patients treated successfully by subpial resection of the U-fibers in 4 gamma, dividing areas 4 and 4S and 6. Walker[17] incised the cerebral peduncle in a case. Talairach[16] produced interruptions at the capsular level. Alpers and Jaeger (cited by Walker[17]) abolished movements by resection of the motor strip in 2 cases. All of these operations left the patient with some paralysis because of interruption of the pyramidal tracts.

Recently, Brown and Walsh[2] reported a case in which hemiballismus was relieved by ventral quadrant section of the cervical cord at C2 level after the method used by Putnam[14] in chorea and athetosis. This interrupts extrapyramidal tracts instead of pyramidal and when properly performed does not produce paralysis. This operation also avoids the disadvantages of cortical operations as noted by Putnam,[15] namely, (1) a higher mortality, (2) postoperative seizures and (3) paralysis of the involved arm and leg. Brown and Walsh's patient—a 73-year-old man—was relieved of his hemiballismus, but died 1 week postoperatively of pulmonary infarcts and bronchopneumonia.

We wish to report a single case of a patient operated on and relieved of hemiballismus after the method used by Brown and Walsh.

CASE REPORT

Mrs. A. R., a 67-year-old hypertensive, was seen on Jan. 24, 1955, because of violent uncontrollable "flailing movements" of the left arm and left leg of 1 day's duration. She had not felt well in the morning. At lunch time, sudden uncontrollable left-sided movements began.

Examination disclosed an elderly woman with a blood pressure of 220/110. There were constant violent flinging movements of the left arm and leg with grimacing of the face. The reflexes were present, equal and active. Her electrocardiogram was abnormal with evidence of old anteroseptal infarction. Heavy sedation did not affect the movements, which became more severe.

On Jan. 31, 1955, a laminectomy of C2 and C3 was done (R.E.S.) after the method suggested by Horrax,[8] and ventral quadrant cordotomy at C2 on the left side was performed, using a knife marked at 4.5 mm. (Fig. 2).

The "flailing" movements ceased postoperatively. A sensory level on the right to just above the clavicle was noted. No weakness or paralysis was noted. An occasional writhing motion of the left arm and grimacing of the face persisted. The 2nd postoperative day she used her left hand and arm to hold and drink her orange juice. She was up in a wheel chair the 2nd day and walked with help 6 days later. Her sensory level at the clavicle persisted at discharge on Feb. 12, 1955.

Films taken postoperatively show her state then. In hemiballismus, it is wise to emphasize that surgery does not cure the underlying disease, but merely stops the violent movements which usually lead to death from exhaustion.

This patient has remained fairly well to date, being able to take care of all her own needs and doing some of her housework. She was examined in Miami on Feb. 18, 1956, while on a vacation. At that time she could not distinguish pin prick 3 inches below the acromion over the whole left arm and below T2 on the chest—in other words C5 and below. Ice could be identified throughout as could light touch, and vibratory and position senses were normal. There was no motor weakness and the reflexes were 3 plus and symmetrical, without Hoffmann or Babinski signs. There was slight facial grimacing. Associated movements of the left arm, such as swinging it while walking, were occasionally absent.

FIG. 2. Postoperative roentgenogram showing level of laminectomy.

SUMMARY

(1) A case of left-sided hemiballismus is reported in which relief without paralysis was obtained by left ventral quadrant cordotomy done at C2 level.

(2) The patient has taken care of most of her own needs and done some housework the past 14 months.

(3) It is wise to emphasize that surgery does not cure the underlying disease but merely stops the distressing movements.

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METASTASES OF CARCINOMA TO MENINGIOMA

D. H. Osterberg, M.D.

Department of Neurology, Harvard Medical School, the Neurological Unit, and the Mallory Institute of Pathology, Boston City Hospital, Boston, Massachusetts

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Metastasis of one tumor to another is very rare. It is the purpose of this communication to present 2 instances of metastasis of carcinoma to meningioma. Three such cases have been found in the literature.[1–3]

In the previously reported cases there were 2 primary breast carcinomas and 1 primary bronchogenic carcinoma. In 1 of our cases, the primary was from bronchus, while in our second case, the histological appearance of the carcinoma pointed to renal cell origin, although neither abdominal operation nor autopsy was done and the renal tumor was never satisfactorily demonstrated by other means.

CASE REPORTS

Case 1. E.J., a 51-year-old white man, was first admitted to Boston City Hospital on Nov. 20, 1939 with a 4-year history of focal seizures involving the left hand and left face and followed by 5–20 minutes of unconsciousness. For the 3 months prior to admission he had noted left-sided weakness.

For 2½ years he had had episodes of sharp pain in his left shoulder and low back.

Examination. A pea-sized left supraclavicular node was found. Power of concentration was poor. There was blurring of the nasal margin of the left disc and slight papilledema on the right. He had a left central facial weakness and left spastic hemiparesis with flexor plantar reflexes. There was reduction of sensation on the left side.

On lumbar puncture the initial pressure was 200; final pressure was 130. There were no cells; total protein was 174 mg. for 100 cc.; colloidal gold and Davies-Hinton reactions were negative. Roentgenograms of the chest were normal. Roentgenograms of the skull were interpreted as showing increased diploic vascularity in the right temporoparietal region and slight thinning of the posterior clinoids. On ventriculography the right lateral ventricle was displaced downward and to the left with its superior border flattened in its middle and posterior portions.

Operation. On Dec. 5, 1939, a right parietal bone flap was turned and a very nodular tumor with soft cystic portions was seen. It was attached to the undersurface of the dura mater approximately over the mid-point of the Rolandic fissure. It was almost completely removed.

Pathological Report. The gross surgical specimen was described as consisting of: (1) A chestnut-shaped piece of tissue measuring 5×5×4 cm., one face in contact with the dura mater. From the part of tumor near the dura mater there projected several papillae which were grossly distinct from the rest of the tumor. The tissue was firm on cut section and varied in color from gray-white to yellow. (2) A small piece of tissue, 1.5×1.0×0.8 cm., similar to the main mass. One face was encapsulated; elsewhere it was bosselated.

Histologic Examination. The microscopic appearance was that of two tissues interdigitating. The first (Fig. 1) was made up of streaming sheets of cells with some tendency to whorl formation and a relatively dense, hyalinized, collagenous stroma containing many blood vessels. The cells in this tissue had well-defined nuclei and poorly defined eosinophilic cytoplasmic envelopes which blended imperceptibly with the surrounding stroma. The nuclei varied in size from about 10–30 mμ and in shape from globular to elliptical. They had a well-defined nuclear membrane and a moderate amount of chromatin material arranged in the

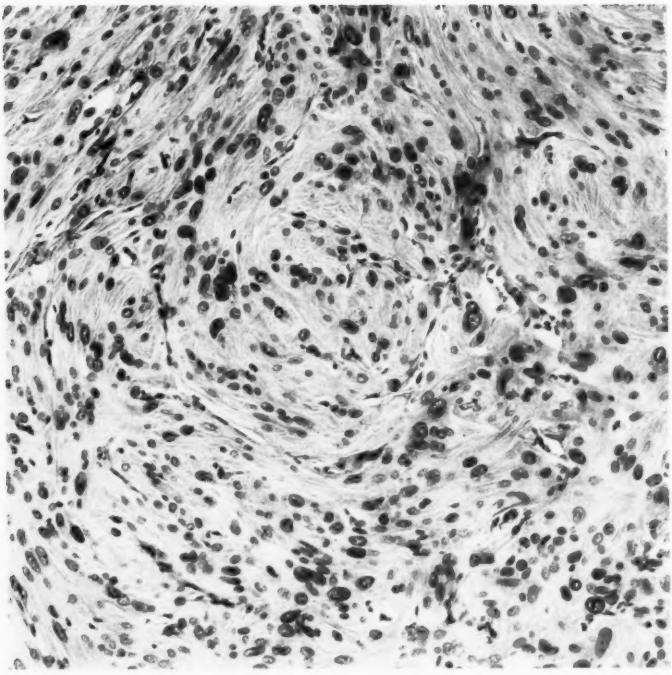

FIG. 1. *Case 1.* Meningiomatous tissue (×200).

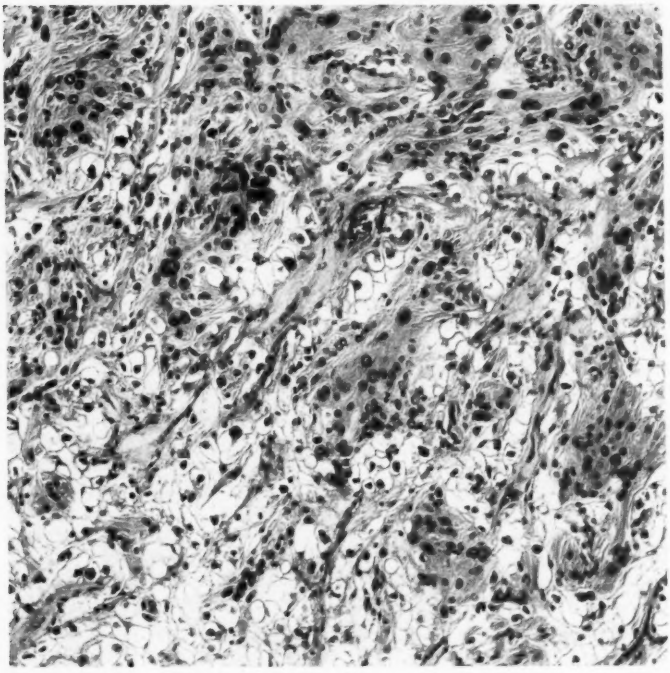

FIG. 2. *Case 1.* Meningiomatous tissue interdigitating with clear vacuolated tumor cells (×200).

peripheral portions of the nuclei in small globules. Many of the nuclei were occupied by one or more faintly basophilic vacuoles. Only rare mitoses were seen in this tissue.

The second tissue (Figs. 2 and 3) was made up of large cells arranged in columns with little stroma. These cells had a very distinct polygonal eosinophilic cytoplasmic membrane. The cytoplasmic contents, however, appeared to be represented by a few strands of eosinophilic material, the remainder of the cytoplasmic space being clear. The nuclei were irregular in shape and occupied about one-tenth of the total cell volume. All the nuclei measured about 10 mμ. There were no mitotic figures. The cells were more densely basophilic than the cells of the first tissue.

Diagnosis: Renal cell carcinoma metastatic to a meningioma.

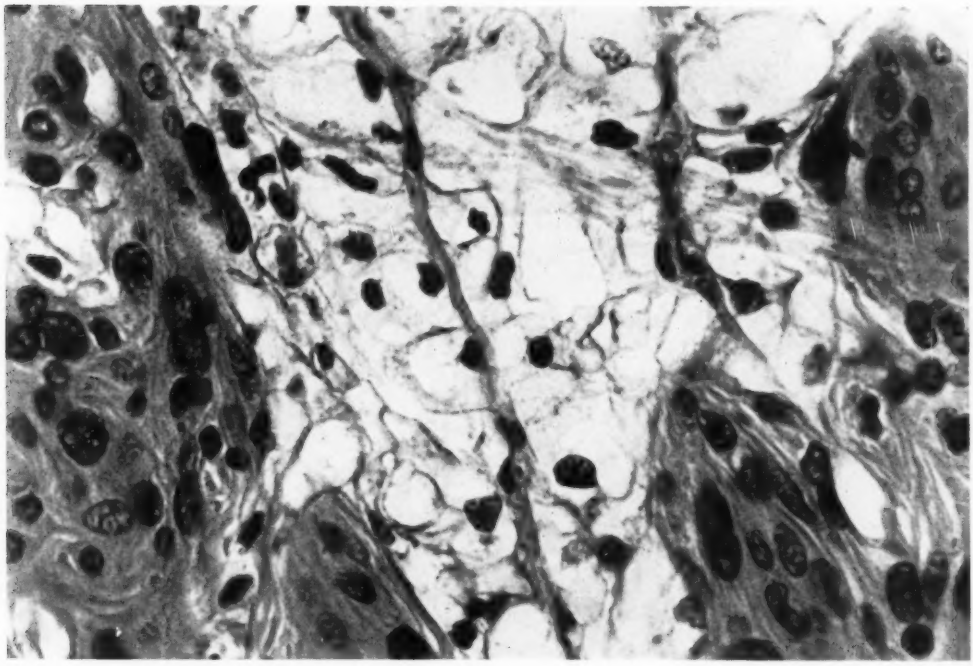

FIG. 3. *Case 1.* Meningioma with finger of metastatic tumor seen in it (×800).

Course. On Dec. 20, 1939, because of the histologic findings, cystoscopy was performed and a benign papilloma of the bladder was found. Retrograde pyelography revealed a kink in the upper third of the right ureter. He was sufficiently improved to be able to return home on Jan. 15, 1940.

He was readmitted to this hospital on July 8, 1940 because of a mass at the site of the craniotomy, which was rapidly increasing in size. He also complained of extreme pain on motion of the left arm.

Examination revealed a large tender mass in the right parietal region. There were 2 D. of papilledema on the right, and blurring of the left disc. There was a left facial weakness. The tongue deviated to the left. The left arm was weak and painful on manipulation. The deep tendon reflexes were increased on the left.

Roentgenograms of the long bones showed no definite evidence of metastasis. By retro-

grade pyelography downward displacement of the left kidney was demonstrated but there was no invasion of the pelvis or calyces. A urological consultant made a diagnosis of probable tumor in the upper pole of the left kidney, but further therapy was not considered justifiable.

The patient was discharged to his home on Aug. 2, 1940 and died 4 days later. Permission for autopsy was not obtained.

Case 2. J.W., a 71-year-old white married male cabinet-maker, was admitted to Boston City Hospital on Oct. 30, 1954 with a chief complaint of generalized weakness and shortness of breath. Dyspnea on exertion had come on rather suddenly 2 weeks prior to admission, and since then weakness had been progressive. For several months he had had a mild cough pro-

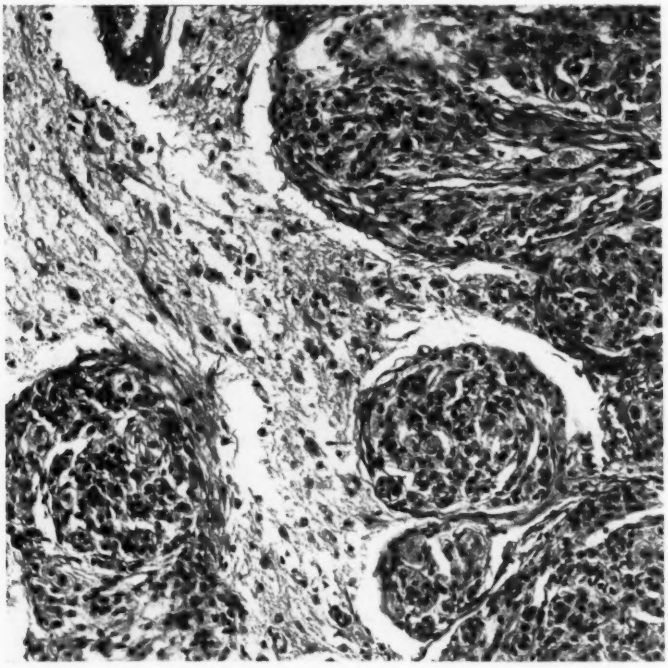

FIG. 4. *Case 2.* Edge of tumor showing digitations into brain tissue and whorl formation (×200).

ductive of occasional blood-streaked sputum. He had smoked twenty cigarettes a day for 50 years.

Examination. There were dullness and decreased breath sounds in the lower half of the right chest, with fine rales at both bases. There was a rough apical systolic murmur.

Roentgenograms of the chest showed a large ill-defined consolidation of the right lower lobe. Biopsy of a right scalene node revealed anaplastic carcinoma.

The lung tumor was considered inoperable. Despite nitrogen mustard and roentgen-ray therapy, the lung lesion increased in size and he died on Feb. 20, 1955.

No neurological abnormalities were recorded.

Autopsy. There was carcinoma of the right lung with extension to the wall of the mainstem bronchus, pericardium, pleura, right half of the diaphragm, heart (auricular wall) and regional lymph nodes. There were metastases to the liver, vertebral and sternal bone marrow, heart, and porta-hepatic, para-aortic, para-esophageal and paravertebral lymph nodes. There

were bilateral pulmonary congestion and edema, mild arteriosclerotic heart disease, splenomegaly (280 gm.), hydrothorax (400 cc.) and ascites (200 cc.).

The formalin-fixed brain showed a firm yellowish-white tumor over the left frontoparietal parasagittal region, 5.0×3.0×2.5 cm. in size, and a depression in the underlying brain, measuring 5.0×2.0×1.3 cm. On section, the tumor consisted of a firm grayish-white vascular tissue which, toward its center, showed a change in color to light gray. The left cerebral hemisphere was edematous. On section, the tumor in the left frontoparietal region was seen to invade both banks of the left Rolandic fissure and to extend down into white matter.

Histologic Examination. There were two distinct tissues. The first consisted of sheets of

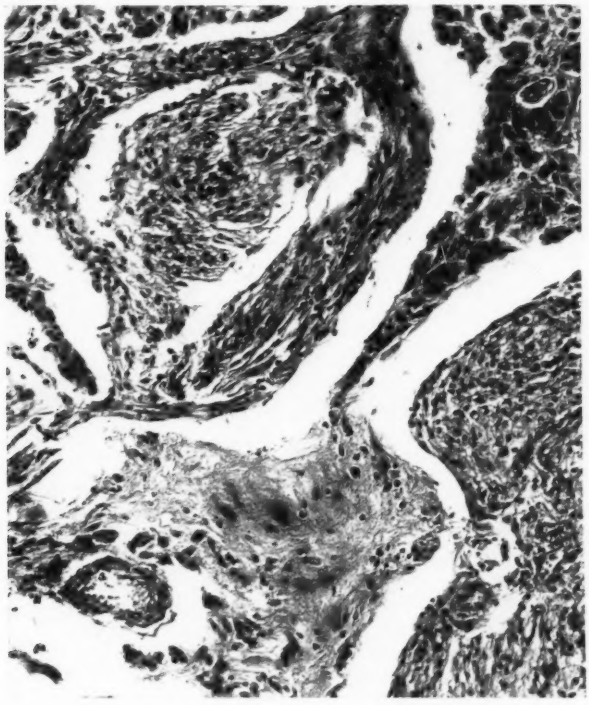

FIG. 5. *Case 2.* Two tumor types interdigitating. The carcinoma extends down from the upper right (×200).

cells with relatively dense stroma and a distinct tendency to whorl formation. Some of the whorls contained a discrete hyaline globule in their center and occasional psammoma bodies. The cells in this tissue had distinct ovoid to globular nuclei and, in the whorls, the nuclei were flattened. There was poor demarcation of the boundaries of the eosinophilic cytoplasm, which blended into the hyaline collagenous tissues of the stroma. The nuclei had a distinct limiting membrane. Their chromatin was gathered in small globules around faintly basophilic vacuoles toward the periphery of the nuclei. There were few mitoses in this tissue, but some multinucleated giant cells were seen. On one side of the specimen, this tissue was seen to thrust finger-like processes into the cerebral cortex (Fig. 4), and the nuclei in these digitations appeared more distinctly basophilic than did those in the more central areas. Some normal-appearing nerve cells were present in the cortex at the base of these projections.

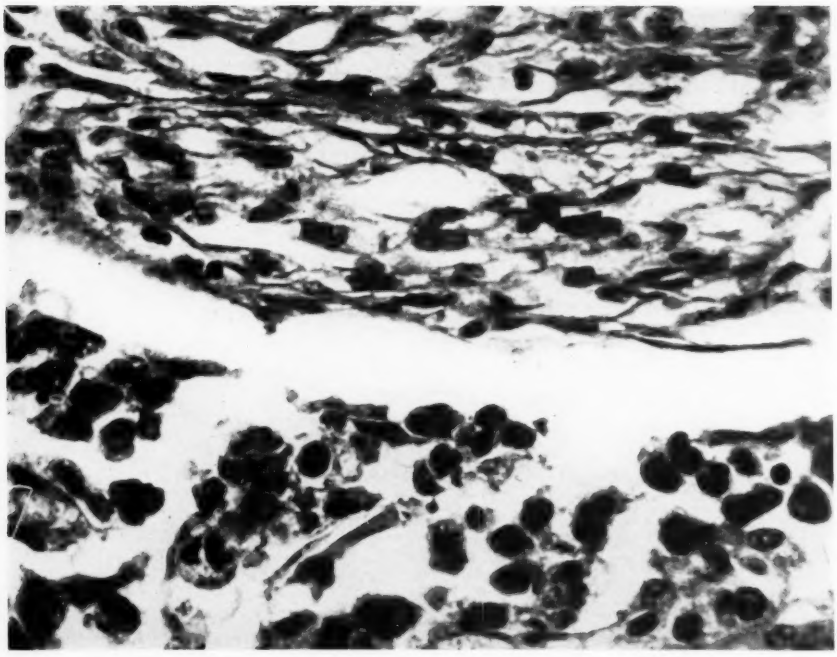

FIG. 6. *Case 2.* The border of the two tumors (×800).

The second tissue (Figs. 5 and 6) was far looser in structure. The dense collagenous stroma appeared to form arborizations around central cores and the cells were more or less adherent to these arborizations. The cells had a relatively distinct eosinophilic cytoplasmic envelope. The nuclei had a definite limiting membrane with relatively large chromatin lumps lying throughout the entire nucleus. There were 1–2 mitoses seen in each high power field. Occasional islands of the first tissue were seen in the second.

Sections of the biopsy from a scalene node, liver, and lung showed an invasive tumor composed of cells exactly similar to those of the second tissue described above.

Diagnosis: Bronchogenic carcinoma with metastasis to a meningioma.

DISCUSSION

Fried[2] reported 1 case of bronchogenic carcinoma metastatic to meningioma; Bernstein[1] and Lapresle *et al.*[3] reported single cases of carcinoma of breast which seeded in a meningioma. Unfortunately in each of these cases the structure of the meningioma is not described in enough detail to compare with our cases. In our cases the meningioma appears more infiltrative or pleomorphic than usual and it is of interest to speculate that this type of "malignant" meningioma might form better "soil" for the implantation of carcinomatous "seeds." The other possibility worthy of speculation, but admittedly unsupported by experimental evidence, it that the "seeds" of a malignant neoplasm may in themselves have the power of transforming a benign neoplasm into one of more malignant type.

These cases are presented primarily because of their rarity and most probably represent a happenstance of metastasis.

SUMMARY

Two cases are presented of carcinoma metastatic to meningioma. Such a rare metastasis was found in only 3 previously reported cases.

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PHANTOM LIMB SYNDROME ASSOCIATED WITH HERNIATED NUCLEUS PULPOSUS

BERNARD E. FINNESON, M.D., HAROLD HAFT, M.D., AND ERICH G. KRUEGER, M.D.
Neurosurgical Section, Veterans Administration Hospital, Bronx, New York

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A review of the literature revealed three contributions dealing with the problem of lumbosacral radiculitis and/or herniated lumbar discs in patients with amputations of the leg. Ricard and Girard[3] described a patient in whom sciatic and causalgic pain developed in a phantom limb 4 years after the amputation. Although a preoperative diagnosis of herniated disc had been made, an extradural cyst of the 5th lumbar nerve root was found instead. This finding seemed to offer a satisfactory explanation for the symptoms present in this case. On the basis of their observation the authors further submitted the hypothesis that the "phantom" may be caused by intraspinal changes (resulting from excessive lumbar motility caused by ambulation with a prosthetic device) involving the nerve roots and causing vasomotor paresthesias and pains.

Perazzini[2] reported 2 cases of herniated nucleus pulposus in leg amputees. In both instances, however, the disc protrusions were verified at operation on the side opposite to the amputation. The author concluded that increased strain on the lumbar spine produced by ambulating with a prosthesis may hasten the onset of symptoms in individuals predisposed to discogenic disease. Since both cases presented a protruded disc opposite to the amputation, the author speculated on the clinical picture in ipsilateral lesions.

Bonica[1] presented an interesting case of a 54-year-old woman who experienced what were apparently symptoms of a herniated nucleus pulposus in 1936. These were described as shooting pains in the back of the thigh radiating to the foot, with aggravation by coughing, sneezing and straining. Her physician injected the sciatic nerve with procaine and later with alcohol. The temporary relief afforded by this procedure was followed by increased pain; in addition to the shooting pain there was now a burning discomfort apparently associated with an alcoholic neuritis. The pain became so severe that an amputation of the lower end of the thigh was performed at the patient's request. She continued to suffer increasingly, and in addition to her previous symptoms there developed a moderately painful phantom limb. During the next 8 years the stump was revised twice, and a rhizotomy and two unilateral cordotomies were performed without effect. Following a detailed neurological examination including myelography, two herniated discs at the 3rd and 4th lumbar interspaces were removed. The severe shooting pain disappeared, yet the phantom sensation associated with mild pain persisted.

CASE REPORTS

Case 1. A 52-year-old white male had an amputation below the right knee for Buerger's disease in November 1945. Following the amputation the patient experienced a painless phantom limb. In July 1948, he fell out of a chair and twisted his back. Several hours later he noted extremely severe pain in the lower back with radiation into the stump and phantom of the right lower extremity. He described the radicular component of his pain as radiating across the posterior aspect of the right buttock and right thigh to the knee, and then along

the posterolateral aspect of the phantom limb as far as the ankle. The pain was aggravated by coughing, sneezing, and straining at stool. One month after onset of his pain the patient was referred to the hospital with the diagnosis of neuroma of the amputation stump.

Examination did not reveal any areas of tenderness at the end of the well-healed stump. The pertinent findings were marked spasm of the paraspinal muscles in the lumbar region bilaterally; extremely severe local pain on compression to the right of the 3rd, 4th, and 5th lumbar spinous processes; and pain on straight leg raising bilaterally, greater on the right. A myelogram confirmed the clinical impression of a herniated nucleus pulposus at the L5-S1 interspace on the right.

In November 1948, an interlaminar excision of this protruded disc was performed. The patient has had no recurrence of his symptoms up to the present time.

Case 2. A 24-year-old white male had onset of stiffness and mild low-back pain associated with radiation of the pain to the left lower extremity in 1950. This persisted until March 1954, when the patient was struck by an automobile, sustaining severe multiple compound comminuted fractures, necessitating amputation of the left lower extremity above the knee. Shortly following the amputation a painful phantom limb developed. There was severe pain in the phantom ankle with extension to the plantar surface of the 1st metatarsal (ball of the foot) and a tingling sensation to all five toes. Occasionally the phantom pain became severe, and at these times he would experience a sensation of the limb being twisted into a distorted position. The low-back pain with radiation into the left leg that the patient suffered prior to his accident returned when he began ambulation with a prosthesis. This was described as pain in the left lower lumbar region, migrating to the buttock, skipping the thigh, and passing from the popliteal space down the posterior aspect of the calf to the ankle. He had no difficulty in differentiating this type of pain from his phantom limb pain. He was admitted in November 1955 for "painful phantom limb."

Examination revealed a well-healed scar at the stump with no local areas of tenderness, a tilted pelvis, spasm of the left lumbar paravertebral muscle and tenderness over the L5 spinous process. The straight leg raising test produced low-back pain on elevation of the right leg, but no pain on elevation of the stump. A filling defect was seen at the L4–L5 interspace on myelography.

In January 1956, an interlaminar excision of a herniated nucleus pulposus at L4–L5 on the left was followed with clinical relief of low-back pain and radiculitis. The painful phantom limb has persisted unchanged.

CONCLUSION

In the 2 cases presented, radicular pain (caused by a herniated nucleus pulposus) and phantom limb symptoms existed simultaneously in the same extremity. The independence of each modality is clearly demonstrated by the postoperative disappearance of the radicular pain with persistence of phantom limb symptoms. This seems to invalidate the notion that mechanical factors involving the spinal nerve roots[3] play a part in the production of phantom limb sensation or pain. Both patients were initially referred to the hospital with a diagnosis other than herniated nucleus pulposus. The coincidence of radiculitis and phantom limb symptoms should be considered in the differential diagnosis. A careful analysis of the pattern of pain may offer a clue to suspect a herniated nucleus pulposus.

The following factors aided in arriving at the diagnosis of herniated nucleus pulposus in the presence of an ipsilateral amputation:

a) The history of a change in the pattern of the "phantom limb" symptoms as well as the appearance of low-back symptoms and signs.

b) The radicular component of the pain was referred to the phantom limb as if projected to the normal dermatome distribution of a specific lumbar or sacral nerve root.

c) The "straight leg raising test" (as executed with the amputation stump) was positive when the amputation was below the knee, but absent when the amputation was above the knee.

d) Myelography confirmed the presumptive clinical diagnosis.

The question whether ambulation with prosthetic devices and the resultant changes in mechanical stresses on the lumbar spine hasten the onset of discogenic symptoms cannot be answered on the basis of available data. In one of our patients radicular symptoms existed prior to the amputation; in the other, the onset of discogenic disease could be related to a specific accidental fall.

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AMYLOID TUMOR OF THE GASSERIAN GANGLION

REPORT OF CASE

DAVID D. DALY, M.D., J. GRAFTON LOVE, M.D., AND MALCOLM B. DOCKERTY, M.D.
Section of Neurology, Section of Neurologic Surgery, and Section of Surgical Pathology, Mayo Clinic and Mayo Foundation, Rochester, Minnesota*

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Tumors of the gasserian ganglion producing trigeminal neuralgia or trigeminal pain are not common[5] and to our knowledge an amyloid tumor of the gasserian ganglion has not been reported previously.

We should like to report a unique case of pain, paresthesias, and loss of sensation in the face produced by an amyloid infiltration of the gasserian ganglion.

REPORT OF CASE

A 42-year-old man was first seen at the Mayo Clinic on March 28, 1956, with the complaint of pain and numbness in the right side of his face. In 1945 he had consulted a dentist after losing a cap from his right upper incisor tooth. The dentist had induced local anesthesia by injection of the right upper alveolar nerve and repaired the tooth. The numbness of the local anesthesia remained. The next day the patient consulted the dentist who was unable to explain the persistent numbness. The patient was treated with injections of thiamine without benefit. Approximately 2 weeks after the onset of the numbness the patient had noted brief, recurrent, lancinating pains in the anesthetic region. These had occurred usually in the evening. In the following years the lancinating pains had decreased in frequency and severity but the patient noted the presence of a persistent, burning, dull pain in the anesthetic region. The part affected by the numbness had slowly increased in size, particularly in the preceding year. The numbness came to extend to below the right eye and over the entire cheek, and the burning pain became severer.

The results of general physical examination were normal. The abnormal findings were limited to the neurologic examination. The right corneal reflex was greatly reduced and the analgesia and anesthesia involved part of the face supplied by the entire 2nd division of the 5th cranial nerve and the superior portion of the 3rd division. The anesthetic region extended to the midline of the bridge of the nose and the upper lip. Weakness or atrophy of the muscles of the face and jaw was not evident.

Routine examinations of the blood and urine gave normal results. The blood serology test for syphilis was nonreactive. Roentgenograms of the skull, including stereoscopic views of the base of the skull, revealed decalcification of the middle fossa on the right side near the petrous tip. Electromyography revealed the motor-unit potentials in the right masseter muscle to be large in amplitude and reduced in number and occasional fibrillation potentials were observed. This was felt to be indicative of neurogenic atrophy.

Because of the history, and neurologic and roentgenographic findings, we made a diagnosis of a tumor involving the right gasserian ganglion. Although the pain that the patient had was of the type usually associated with trigeminal neuralgia, which of course has an unknown etiology, the objective neurologic findings indicated a lesion that was destructive of nerve fibers. Operation for removal of the tumor of the gasserian ganglion was advised. The patient was told prior to operation that he was expected to have more "numbness" rather than less of the right side of the face after operation, for the surgical extirpation of a tumor involving

* The Mayo Foundation, Rochester, Minnesota, is a part of the Graduate School of the University of Minnesota.

the gasserian ganglion usually necessitates removal of part or all of the gasserian ganglion with division of the posterior sensory root.

On April 2, 1956, with the patient under the effects of intratracheal anesthesia and in the upright position, subtemporal craniectomy was performed on the right side through a small perpendicular incision $\frac{3}{4}$ inch anterior to the tragus; the middle meningeal artery was silver-clipped and divided, and the dura mater was stripped from the 3rd branch of the gasserian ganglion and from the gasserian ganglion as is done when the posterior root of the ganglion is to be exposed for root section for trigeminal neuralgia. Immediately it was noticed that the exposed portions of the 2nd and 3rd branches and the ganglion itself bulged convexly toward the craniectomy, and these structures appeared yellower than normal, not unlike the gross picture of a neurofibroma. The capsule of the ganglion was incised and the tumor, which was

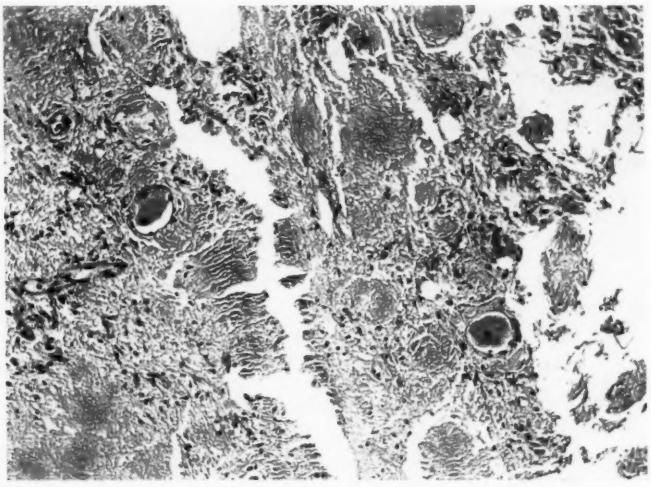

FIG. 1. Amyloidosis of gasserian ganglion and its afferent nerve trunks. The granular homogeneous areas devoid of nuclei represent the amyloid deposits (hematoxylin and eosin, ×125).

under pressure, began to separate the fibers; it appeared slightly darker than the ganglion but not so dark as a meningioma. The tissue, which had a gross appearance not unlike that of an epidermoid,[4] was gradually removed piecemeal. By means of a small curet it was possible to scoop out the neoplastic tissue not only from the mesial side of the 2nd and 3rd branches and the ganglion but also from the mesial side of the posterior root and over the tip of the petrous bone just beneath the tentorium. In removing the tumor it was necessary to sacrifice the sensory and motor roots of the ganglion. Several pieces of Gelfoam were left extradurally to control some of the oozing about the ganglion and then the wound was closed in layers without drainage.

Grossly the tissue removed was larger in amount than that from the usual "tic" operation. Microscopic verification of such tissue is routine in our laboratory and accordingly the material was sectioned immediately on a fresh-freezing microtome and stained with Terry's polychrome methylene blue. This stain exhibits a beautiful metachromatic effect with amyloid and the diagnosis of amyloidosis was immediately rendered to the surgeon.

Permanent sections made from frozen and paraffin blocks and stained routinely with hematoxylin and eosin, with Congo red, and with methyl violet brought out the characteristics depicted in the accompanying photomicrographs (Figs. 1–4). At least 50 per cent of both the ganglion and its afferent nerve bundles was replaced by a substance having all the

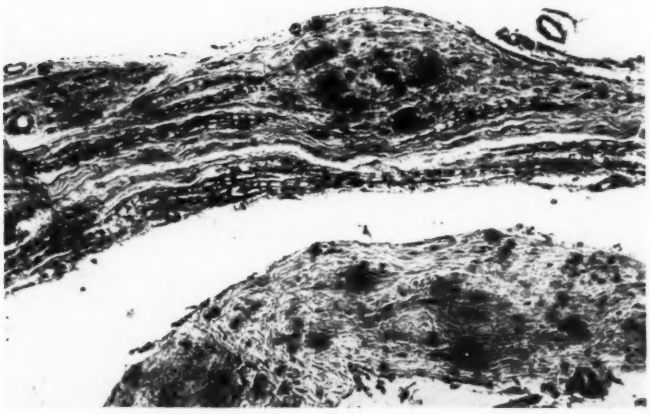

FIG. 2. Interruption of continuity of nerve bundles by a tumefactive nodule of amyloid material (hematoxylin and eosin, ×150).

staining characteristics of amyloid.[5] The material was homogeneous and amorphous, and it occurred focally and in irregularly outlined sheets. Small nodular accumulations of it expanded the nerve trunks, and the fibers of the nerve trunks lost their identity as they coursed through the deposits.[4] Ganglion cells were surrounded and occasionally invaded.[2] Others appeared to have degenerated as a result of ischemia from amyloidosis of their nutrient vessels. The nutrient vessels, surprisingly enough, showed irregular involvement with intact

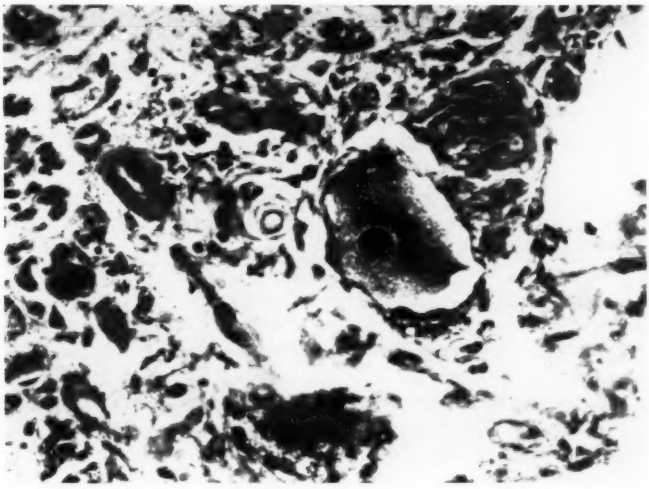

FIG. 3. Details of a ganglion cell partially surrounded by amyloid (hematoxylin and eosin, ×400).

vessels exhibiting wide open lumens and others whose mural coats had been thickened and replaced lying side by side.[7] On the basis of the available material the presenting picture appeared to represent primary parenchymatous involvement rather than secondary encroachment from the adventitia of blood vessels. In this aspect the case is most unusual.

The patient's convalescence was uneventful, and he was allowed to leave the hospital and go directly to his home on the 3rd day after operation, at which time the apposition sutures had been removed. A dry dressing was applied which was to be discarded at home. A postoperative neurologic examination revealed complete anesthesia in the distribution of the right 5th cranial nerve with weakness of the masseter, temporal, and pterygoid muscles on the same side.

The patient was re-examined on June 7, 1956, at which time his condition was satisfactory. He was relieved of the pain that he had had prior to surgical intervention; the neurologic status was the same as it was immediately after operation.

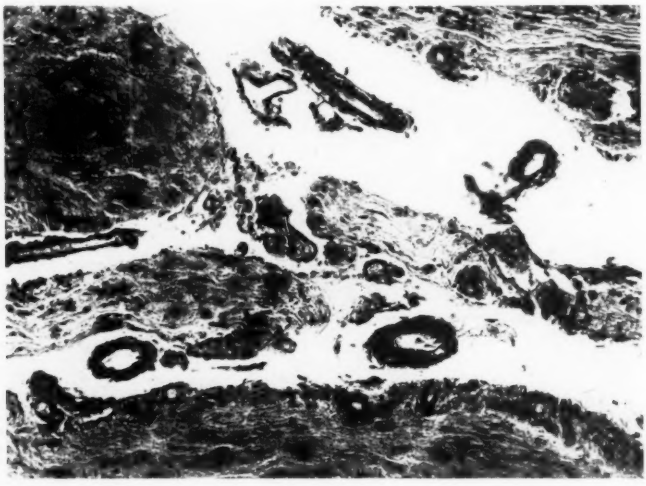

FIG. 4. Spotty distribution of amyloid affects only certain of the blood vessels, the invaded walls of which appear thick and dense (hematoxylin and eosin, ×150).

COMMENT

More than 100 years ago Virchow coined the term "amyloid" to describe the starchlike substance present in many of the organs of persons dying from the effects of what previously had been termed "lardaceous disease." The condition was generalized or systemic and although the cause was, and still remains, obscure, it was regarded as being secondary because it almost always occurred as a late complication of chronic, debilitating, inflammatory conditions, such as osteomyelitis, tuberculosis, syphilis and the like. Parenchymatous organs such as the liver, the kidneys and the adrenal glands were the chief targets in this commonly observed form of amyloidosis.

In primary amyloidosis a substance having the same chemical and staining reactions as the material found in lardaceous disease is observed infiltrating mesenchymal tissues such as smooth and striated muscle, cardiac muscle, and muscles of the tongue, the spleen and other organs. Cardiac failure resulting from replacement

of contractile elements by infiltrates of amyloid substance is often a terminal event in patients so afflicted. Antecedent or associated conditions cannot be discovered in contradistinction to those seen in the secondary form—hence the designation "primary amyloidosis." Unlike secondary amyloidosis the primary variety is occasionally limited in distribution rather than diffuse.

Still another type of amyloid degeneration is observed in patients afflicted with multiple myeloma of bone. This type has been separated from the afore-mentioned secondary variety for, although it occurs as a consequence of the myeloma, the distribution of amyloid deposits follows the pattern set in the primary form of the disease. The amyloid material also is found rather frequently in the form of deposits within the myelomatous masses themselves and it may indeed be limited to these sites in cases of amyloidosis with myeloma.

Lastly, amyloid can occur as localized tumorous deposits which are solitary or occasionally multiple and which occur without the systemic effects of the three other forms of the disease. The upper respiratory passages and the urinary bladder account for the great majority of these amyloid tumors, the origin of which is just as obscure as the cause of amyloidosis in general.

The nervous system, both central and peripheral, enjoys a strong relative immunity to amyloid disease which is difficult to understand. Amyloid tumors of the brain have been reported by Fischer and Holfelder.[2] Their patient had had previous therapy for squamous cell carcinoma of the right temporal region and the amyloidosis was considered to be secondary in nature. In the case reported by Saltykow[7] three amyloid nodules were present in a brain which had been sent to him for examination. Whether these nodules represented primary or secondary forms of the disease or whether indeed they were localized amyloidomas we do not know. Bürgi[1] observed cerebral invasion from an amyloid tumor of the parietal bone. From our experience we would judge that this represented the amyloidosis of myeloma, having observed an entire rib replaced by amyloid substance in a comparable case. Morgenstern's[6] observation of amyloid substance in the blood vessels surrounding a nodular sarcoma which had thickened the parietal bone and invaded the brain may have status comparable to that of Bürgi's case. We have been unable to verify Morgenstern's reference to a case reported by Schwarz[8] of a cerebral amyloidoma in a patient with jacksonian epilepsy.

As regards peripheral nerve involvement in amyloidosis, emphasis is directed to the ischemic degeneration of these nerves as a consequence of occlusion by amyloid material of the blood vessels supplying them. Only rarely does the amyloid substance envelop, infiltrate, and destroy nerve structures. For the occasional exception to this rule the reader is referred to the 1942 review by Kernohan and Woltman.[3]

The present report concerns an unusual instance of trigeminal neuralgia in which the etiologic basis consisted of extensive replacement of the gasserian ganglion and its afferent nerve roots by amyloid substance.

It is most interesting that the results of subsequent studies on this patient were negative for the usual causes of amyloidosis. There was no evidence for myeloma. The existence of primary systemic amyloidosis was ruled out by the absence of a large tongue, a normal electrocardiographic tracing, and other signs of mesenchymal involvement. Paunz' test with Congo red gave negative results. Between the two remaining possibilities, namely, amyloid tumor and a circumscribed form of primary amyloidosis, we cannot choose with discretion. We wish merely to present the unusual features of nerve-tissue involvement by amyloid substance.

SUMMARY

An unusual case is presented in which trigeminal neuralgia was produced by amyloid deposits in the gasserian ganglion and its afferent nerve roots. Involvement of nutrient vessels was not a prominent feature. Evidence is presented to show that the process was not part of a generalized condition, as exemplified by the well-known primary and secondary categories of "lardaceous disease."

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INTRAMEDULLARY EPIDERMOID TUMOR OF THE SPINAL CORD

ARTHUR B. KING, M.D.
Department of Neurosurgery, Guthrie Clinic, Sayre, Pennsylvania

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Among the most uncommon neoplasms involving the central nervous system are those that arise from retained remnants of skin. Just how these dermal elements get misplaced is not entirely clear. Embryologic studies of the prenatal development of the neural canal indicate at least one possible mechanism but it is still difficult to account for all the facts presented by a tumor composed of integument and its appendages found deeply imbedded within the brain and spinal cord.

The case history to be presented is that of an epidermoid tumor found in the substance of the thoracic portion of the spinal cord.

CASE REPORT

No. B-177286. J.R.W., a 42-year-old male, was admitted to the hospital in June 1955. Approximately 1 year before, without apparent reason, tingling sensations developed in his right leg and he noticed difficulty in arising from the sitting position. It then became apparent that the right leg was getting progressively weaker. About March 1955 the leg had lost so much strength that it was almost impossible to climb stairs. Spontaneous "jerking movements" of the leg occurred about this time and were most prominent at night.

For the last 3 months the patient complained of a constant dull ache in the mid-dorsal region which was aggravated by lifting and bending, but not by coughing or sneezing. Neither chiropractic nor osteopathic treatments provided any relief. Since the onset of the backaches, numbness had been present in the posterior aspect of the right thigh. The patient had no complaints referable to the proper functioning of the urinary bladder. Extensive study at another hospital, including roentgenograms of the back and a lumbar puncture, failed to disclose the source of the complaints.

Physical examination, except for the neurologic findings, was within normal limits. The patient appeared to be in excellent health and had surprisingly little discomfort. There were no abnormalities noted of the cranial nerves or of the arms. Motion of the back was excellent and there was no tenderness on percussion. Careful examination of the entire back failed to reveal an indentation in the skin that would suggest a congenital dermal sinus. The left abdominal reflexes were absent. The right leg was definitely weak. The tone of the muscles, if anything, was diminished. There was no atrophy of the muscles. The patient could stand on this leg alone but did not have sufficient strength to flex the knee while so standing, or to come up on his toes. Definite ataxia was present in the right leg and position sense was almost absent. Much less ataxia was noted in the left leg and position sense was intact. Pain sensibility was intact bilaterally. Only an indefinite area of hypesthesia to touch was present over the back of the right leg, in the area of numbness. There was pronounced increase in the tendon reflexes of the right leg and bilateral Babinski response.

Myelography disclosed a mass at the level of T6 which produced an almost complete block. The mass was elliptical, smoothly outlined in the center of the canal, and appeared to be an intramedullary tumor.

Operation. Laminectomy disclosed such a neoplasm. When the spinal cord was exposed a small mass, about the size of a garden pea, was seen projecting out of the dorsal column, just to the left of the midline. The mass had a white, glistening cast. The cord itself was diffusely swollen for about two segments. As dissection was attempted, an exceedingly thin

surrounding membrane ruptured and cheesy necrotic material, characteristic of that seen in sebaceous cysts, began to extrude. This material was gently lifted out, leaving a defect about 5 mm. in width and about 1.5 cm. in length in the central part of the cord. Several flecks of calcium were seen in the wall of the cavity after removal of the soft contents. A portion of the thin capsule which was attached to one of the dorsal roots was removed for microscopic study. No attempt was made to remove the lining of the cyst since it was firmly attached to the substance of the cord, and it could not be easily stripped off without doing considerable damage to the remaining neural tissue.

The *pathologist's report* is quoted verbatim: "Sections of the tiny fragments of the soft red tissue received reveal it to be composed almost completely of myelinated nerve fibers and small blood vessels. However, covering one surface of the larger fragments is a thick eosinophilic-staining layer of homogeneous material which appears to be a completely hyalinized layer of tissue, which may have been at one time a layer of stratified squamous epithelium (Fig. 1). This hyalinized layer contains considerable calcium deposits but there is no recog-

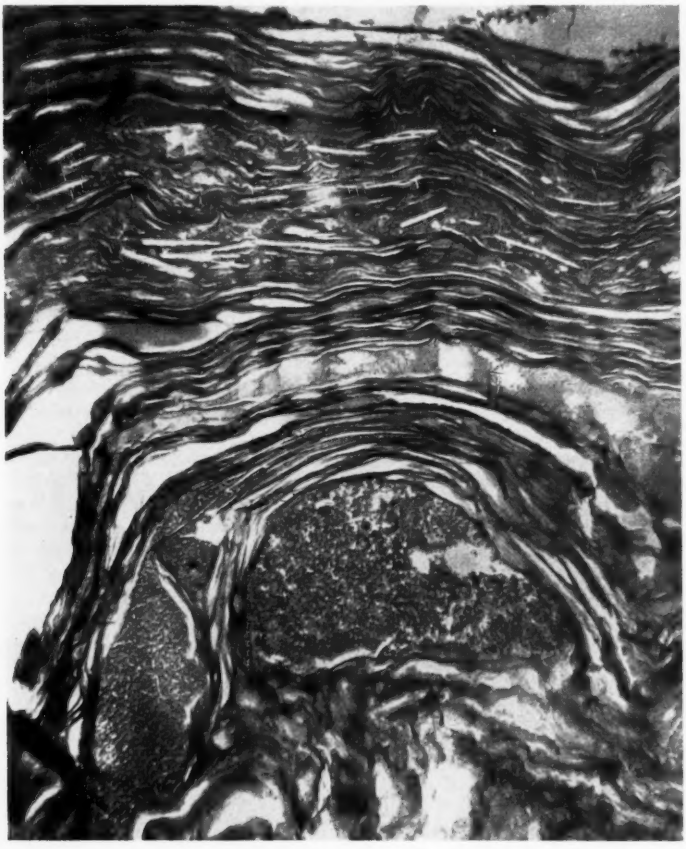

FIG. 1. Photomicrograph of section through the wall of the tumor mass, showing the laminated layers of hyalinized material and masses of necrotic sebaceous material. Viable epithelium was not seen in any of the material removed at operation.

FIG. 2. Photomicrograph showing clefts found in the sebaceous material, typical of cholesterol deposits.

nizable epithelium present and, of course, there is no evidence of any skin appendages. Numerous sections of the soft, yellowish-white material described grossly reveal it to have the typical appearance of keratin. It is composed of numerous wave-like layers of acidophilic, basophilic and polychromatic material which in some regions is extremely fragmented, suggesting the appearance of falling leaves so typical of the so-called sebaceous material. Focal regions of calcification are also present as are numerous elliptical-shaped clefts typical of spaces left by cholesterol deposits (Fig. 2). The above features are consistent with the diagnosis of an epidermal inclusion cyst of long duration but there is no identifying stratified squamous epithelium present. It is quite conceivable that it could have been destroyed because of the chronicity of the lesion. No evidence of malignancy is noted. The possibility of the so-called cholesteatoma must not be forgotten. Diagnosis: Consistent with epidermal inclusion cyst of spinal cord."

Course. During the past year the patient has shown steady progress in his ability to walk. He can walk without support but does like to carry a cane for reassurance. Walking up stairs is still a problem. There are no sphincteral difficulties and he is not conscious of any sensory disturbances in the legs. The pain in the back has disappeared. Spontaneous clonus of both feet is troublesome at night.

There is a foot drop on the right and 1-inch atrophy of the calf. The quadriceps muscle is about 75 per cent of normal strength. Voluntary movement is excellent in the knee and hip but is very limited at the ankle and toes. Strength and precision movements of the left leg are about normal.

The tendon reflexes at both the knees and ankles are very hyperactive. Clonus can be elicited on the right and the great toes of both feet show dorsiflexion on plantar stimulation. Touch and position sensibility are normal but on the left there is loss of pain and temperature appreciation to the level of T6, as noted immediately after operation. There is no limitation of motion of the back. He has returned to his work as a gasoline station attendant.

DISCUSSION

Epidermoid tumors occur in the vertebral axis very uncommonly. It has not been possible to determine the exact number but there are probably less than 50 reported cases. Excellent surveys of the medical literature have been published by Peyton and Baker,[4] Naffziger and Jones,[3] and King.[1]

Congenital dermal sinuses, which are probably a variant of the same general embryological deficiency, are being recognized with increasing frequency and the subject has been well summarized by Matson and Ingraham.[2] Multiple tumors are of extreme rarity but such a case was described by Raskin.[5]

Tumors of this group occurring in the spinal region are commonly subdural but rarely intramedullary. Also, the lumbar region with the tumor among the cauda equina, appears to be a favorite site. Reports of an intramedullary tumor in the mid-dorsal region, similar to the case described, have not been uncovered although our efforts have not been exhaustive. Naffziger and Jones[3] reported 2 instances in which the neoplasm was within the filum terminale but did not seem to invade the conus.

There was nothing preoperatively that directed attention toward the diagnosis of an epidermoid tumor. There were no roentgen-ray findings indicating destruction of the dorsal lamina or pedicles. Calcification was not present within the canal. Gross calcification within epidermoid tumor was formerly thought to be rare, but Peyton and Baker[4] reported several cases in which it was present and it has been noted often since. I have not found any cases of such tumors occurring in the spinal canal in which there were sufficient calcium deposits to be noted radiologically. In the patient described above, small flecks of calcified material within the tumor could be seen macroscopically at operation, and these are easily visible under the microscope. However, they were too few and too small to be seen by roentgen ray.

Aseptic meningitis, which follows release of cholesterol crystals into the subarachnoid space, has been encountered by several authors on this subject. In this instance, no history of such an occurrence was obtained and no crystalline material was noted in the spinal fluid obtained at the time of myelography. The myelograms obtained after the instillation of subarachnoid Pantopaque suggested an intramedullary neoplasm but otherwise did not appear characteristic of anything.

As has been noted by several authors, the capsule of the epidermoid was densely adherent to the surrounding neural structures and it was also exceedingly thin, another general finding. Rather than produce additional damage to the spinal cord, which had been reduced to a shell of a few millimeters in thickness, no serious attempt was made to remove the capsule and I could not uncover a plane of cleavage from the neural tissue.

Microscopic sections indicate that the tumor contents were only hyalinized material. Frequently the loss of the growing layer is noted in epidermoid cysts elsewhere, presumably because of prolonged pressure by the intracystic contents. It is hoped that this has occurred here. King[1] has reported a recurrence in the lumbar region when part of the capsule was left adherent to the cauda equina. All evidence points toward a very slow growth by these neoplasms and if they do recur, it may be many years after the initial partial removal.

SUMMARY

The occurrence of an intramedullary epidermoid tumor of the spinal cord in the mid-dorsal region is reported. There were no special features of the clinical course

that indicated the nature of the neoplasm preoperatively. Complete excision did not appear feasible. Recovery has been incomplete but there are no signs of recurrence 1 year after operation.

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NOTICES

AMERICAN ACADEMY OF NEUROLOGICAL SURGERY AWARD

The Second Annual Award of the American Academy of Neurological Surgery was presented to Dr. Hubert L. Rosomoff of Bethesda, Maryland, for his paper entitled "Hypothermia and Cerebral Vascular Lesions. II. Experimental Middle Cerebral Artery Interruption Followed by the Induction of Hypothermia."

The Academy announces its Third Annual Award. This award is intended as an incentive to research by younger neurosurgeons. It is given for the best paper submitted reporting original clinical or laboratory research pertaining to the nervous system for which the author has had the principal responsibility. Eligibility is confined to doctors of medicine currently in training in neurological surgery or who have completed their training since June 30, 1955. Those who have been certified by the American Board of Neurological Surgery, or are Fellows of the Royal College of Surgeons, Canada, subspecialty neurosurgery, or have other equivalent certification are not eligible. The paper shall not have been accepted for publication in any journal, but may have been submitted as a thesis for a degree. When subsequently published, it shall carry the footnote, "American Academy of Neurological Surgery Award, 1957."

The recipient of the Third Award will present his paper at the 19th Annual Meeting of the Academy at The Cloister, Sea Island, Georgia, November 11–13, 1957. His expenses while attending the meeting and his travel expenses to and from his home (if living outside the North American Continent, from the port of entry into the United States) will be borne by the Academy. In addition, there will be an honorarium of one hundred dollars.

Manuscripts to be considered by the Award Committee should be sent to Dr. Eben Alexander, Jr., Bowman Gray School of Medicine, Winston-Salem, North Carolina, before July 15, 1957. A resume of the candidate's postdoctoral training must accompany the paper when submitted.

AMERICAN NEUROLOGICAL ASSOCIATION

The 82nd annual meeting of the American Neurological Association will be held at the Claridge Hotel, Atlantic City, New Jersey, June 17–19, 1957 under the Presidency of H. Houston Merritt, M.D. of New York City.

All communications regarding the meeting should be addressed to Charles Rupp, M.D., Secretary of the Association, 133 South 36th Street, Philadelphia 4, Pennsylvania.

ASSOCIATION FOR RESEARCH IN NERVOUS AND MENTAL DISEASE

At the 36th annual meeting of the Association for Research in Nervous and Mental Disease held in New York City on December 7 and 8, 1956, the following officers were elected for the year 1957: President, Dr. Francis J. Braceland; First Vice-President, Dr. Paul Hoch; Second Vice-President, Dr. Carl Pfeiffer; Secretary-Treasurer, Dr. Rollo J. Masselink; Assistant Secretary, Dr. Lawrence C. Kolb.

The 37th annual meeting will be held at the Hotel Roosevelt in New York City on December 13 and 14, 1957. The topic will be "The Effect of Pharmacologic Agents on the Nervous System."

CONGRESS OF NEUROLOGICAL SURGEONS

The 7th annual meeting of the Congress of Neurological Surgeons will take place at the Statler Hotel in Washington, D. C., Nov. 7–9, 1957. The entire program will be devoted to the subject of Pediatric Neurosurgery.

Officers of the Society are: President, Dr. Frederick C. Rehfeldt; Vice-President, Dr. Raymond K. Thompson; Secretary-Treasurer, Dr. Philip D. Gordy.

HARVEY CUSHING SOCIETY

The Twenty-Fifth Anniversary meeting of the Harvey Cushing Society was held at the Statler Hotel, Detroit, Michigan, April 25–27, 1957. The following officers were elected: President, Howard A. Brown, San Francisco; President-Elect, Bronson S. Ray, New York; Vice-President, Wallace B. Hamby, Buffalo; Secretary, David L. Reeves, Santa Barbara; Treasurer, Hendrik J. Svien, Rochester, Minn.; Historian, Louise Eisenhardt, New Haven; Member of Executive Committee, Leo M. Davidoff, New York.

The following were appointed to the Membership Committee: Edmund J. Morrissey, San Francisco, Chairman; Frank P. Smith, Rochester, N. Y., and Harold R. Oberhill, Chicago.

Members of the Program Committee for 1958 are: J. Douglas French, Long Beach, Chairman; Edwin B. Boldrey, San Francisco, C. Hunter Shelden, Pasadena, and Arthur A. Ward, Seattle.

Mrs. Eben Alexander, Jr., Winston-Salem, is President of the Ladies Auxiliary, and Mrs. Dean H. Echols, New Orleans, is President-Designate.

The next meeting of the Society will be in Washington, D. C., at the Mayflower Hotel, April 21, 22 and 23, 1958.

NEUROSURGICAL SOCIETY OF AMERICA

The 10th annual meeting of the Neurosurgical Society of America was held at Palm Springs, California, January 16–19, 1957. The following officers were elected: President, Dr. Lyle A. French; Vice Presidents, Dr. Harvey Chenault and Dr. Frank E. Nulsen; Secretary, Dr. Frank P. Smith; Treasurer, Dr. Bertram Selverstone.

The next meeting of the Society will be held in Key Biscayne, Florida, January 15–18, 1958 and is intended for the members and invited guests.

NEW YORK SOCIETY OF NEUROSURGERY

The next meeting of the New York Society of Neurosurgery will be held at 8:30 P.M. on May 21, 1957, at the New York Academy of Medicine.

At this meeting the annual Charles A. Elsberg Lecture will be presented by Dr. R. Eustace Semmes of Memphis, Tennessee.

MEETINGS

American Academy of Neurological Surgery, The Cloister, Sea Island, Georgia, November 11–13, 1957. Eben Alexander, Jr., Bowman Gray School of Medicine, Winston-Salem, N. C., Secretary.

American Neurological Association, Claridge Hotel, Atlantic City, N. J., June 17–19, 1957. Charles Rupp, 133 South 36th St., Philadelphia 4, Pa., Secretary.

Association for Research in Nervous and Mental Disease, Hotel Roosevelt, New York, N. Y., December 13–14, 1957. Rollo J. Masselink, 710 West 168th St., New York 32, N. Y., Secretary.

Congress of Neurological Surgeons, Statler Hotel, Washington, D. C., November 7–9, 1957. Philip D. Gordy, Suite B-1, Professional Bldg., Wilmington, Del., Secretary.

First International Congress of Neurosurgery, Brussels, Belgium, July 21–28, 1957. Dr. Marcel David, Hospital Ste. Anne, Paris, Secretary-General, and Dr. William B. Scoville, 85 Jefferson St., Hartford, Conn., Assistant Secretary-General.

Harvey Cushing Society, Mayflower Hotel, Washington, D.C., April 21–23, 1958. David L. Reeves, 316 West Junipero St., Santa Barbara, Calif., Secretary.

Latin-American Congress of Neurosurgery, University of Antioquia, Medellín, Colombia, July 8–11, 1957. Dr. Ernesto Bustamante, Facultad de Medicina, Medellín, Colombia, Secretary.

Neurosurgical Society of America, Key Biscayne, Florida, January 15–18, 1958. Dr. Frank P. Smith, 260 Crittenden Blvd., Rochester 20, N. Y., Secretary.

New York Society of Neurosurgery, New York Academy of Medicine, New York, N. Y., May 21, 1957. Dr. Henry Wigderson, 162-05 89th Ave., Jamaica 32, N. Y., Secretary.

Society of British Neurological Surgeons, Royal College of Physicians of Ireland, Dublin, Ireland, May 16–18, 1957 (in conjunction with the Irish Ophthalmological Society). Mr. D. W. C. Northfield, London Hospital, London E.1, England, Secretary.

Society of Neurological Surgeons, St. Louis, Mo., May 17–18, 1957. Dr. Bronson S. Ray, 525 East 68th St., New York 21, N. Y., Secretary.

CORRESPONDENCE

SHERRINGTON CENTENARY

To the Editor:—This is the centenary year of the birth of Sir Charles Scott Sherrington, O.M., a founder and main architect of the physiology of the nervous system. The Royal Society of Medicine, wishing to pay tribute to his life and work, proposes to raise a fund towards a Sherrington Lecture, for the furtherance of knowledge on the nervous system, to be delivered from time to time in the Society's rooms in London.

It is felt that many will wish to contribute: both those who were his friends, pupils and colleagues, and those, more numerous, who, as patients, doctors and scientists, have benefited indirectly from his work.

We wish to take this opportunity to commend the endeavour of the Royal Society of Medicine to establish this memorial to a great pioneer in scientific medicine.

Donations should be made payable to the Secretary, The Royal Society of Medicine, 1 Wimpole Street, London, W.1, and cheques crossed "Sherrington Memorial."

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The *Journal of Neurosurgery* is devoted to the publication of work relating primarily to neurosurgery, including studies in clinical neurophysiology, organic neurology, ophthalmology, radiology and pathology. Short articles on unusual cases and on technique, special instruments or equipment that might be useful to others in the field are also acceptable.

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